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(54) Title: METHODS OF DIAGNOSIS AND PROGNOSIS OF OVARIAN CANCER

(57) Abstract: The present invention provides novel genes and proteins for diagnosing ovarian cancer and/or a likelihood for survival, or recurrence of disease, wherein the expresson of the genes and proteins is up-regulated or down-regulated or associated with the occurrence or recurrence of a specific scanner sub-type. The ovarian cancer-associated genes and proteins of the invention are specifically exemplified by the genes and proteins set forth in Tables 1 to 3 and the Sequence Listing.

METHODS OF DIAGNOSIS AND PROGNOSIS OF OVARIAN CANCER

Field of the invention

The present invention relates to the identification of nucleic acid and protein expression profiles and nucleic acids, products, and antibodies thereto that are involved in ovarian cancer; and to the use of such expression profiles and compositions in the diagnosis, prognosis and therapy of ovarian cancer. More particularly, this invention relates to novel genes that are expressed at elevated or reduced levels in malignant tissues and uses therefor in the diagnosis of cancer or malignant tumors in human subjects. This invention also relates to the use of nucleic acid or antibody probes to specifically detect ovarian cancer cells, such as, for example, in the ovarian surface epithelium, wherein over-expression or reduced expression of nucleic acids hybridizing to the probes is highly associated with the occurrence and/or recurrence of an ovarian tumor, and/or the likelihood of patient survival. The diagnostic and prognostic test of the present invention is particularly useful for the early detection of ovarian cancer or metastases thereof, or other cancers, and for monitoring the progress of disease, such as, for example, during remission or following surgery or chemotherapy. The present invention is also directed to methods of therapy wherein the activity of a protein encoded by a diagnostic/prognostic gene described herein is modulated.

Background of the invention

1. General

As used herein the term "derived from" shall be taken to indicate that a specified integer are obtained from a particular source albeit not necessarily directly from that source.

Unless the context requires otherwise or specifically stated to the contrary, integers, steps, or elements of the invention recited herein as singular integers, steps or elements clearly encompass both singular and plural forms of the recited integers, steps or elements.

The embodiments of the invention described herein with respect to any single embodiment shall be taken to apply *mutatis mutandis* to any other embodiment of the invention described herein.

Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated step or element or integer or group of steps or elements or integers but not the exclusion of any other step or element or integer or group of elements or integers.

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations or any two or more of said steps or features.

The present invention is not to be limited in scope by the specific examples described herein. Functionally equivalent products, compositions and methods are clearly within the scope of the invention, as described herein.

The present invention is performed without undue experimentation using, unless otherwise indicated, conventional techniques of molecular biology, microbiology, virology, recombining DNA technology, peptide synthesis in solution, solid phase peptide synthesis, and immunology. Such procedures are described, for example, in the following texts that are incorporated herein by reference:

1. Sambrook, Fritsch & Maniatis, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratories, New York, Second Edition (1989), whole of Vols I, II, and III;
2. DNA Cloning: A Practical Approach, Vols. I and II (D. N. Glover, ed., 1985), IRL Press, Oxford, whole of text;
3. Oligonucleotide Synthesis: A Practical Approach (M. J. Gait, ed., 1984) IRL Press, Oxford, whole of text, and particularly the papers therein by Gait, pp1-22; Atkinson *et al.*, pp35-81; Sproat *et al.*, pp 83-115; and Wu *et al.*, pp 135-151;
4. Nucleic Acid Hybridization: A Practical Approach (B. D. Hames & S. J. Higgins, eds., 1985) IRL Press, Oxford, whole of text;
5. Perbal, B., A Practical Guide to Molecular Cloning (1984);
6. Wünsch, E., ed. (1974) *Synthese von Peptiden in Houben-Weyls Metoden der Organischen Chemie* (Müler, E., ed.), vol. 15, 4th edn., Parts 1 and 2, Thieme, Stuttgart.

7. Handbook of Experimental Immunology, Vols. I-IV (D. M. Weir and C. C. Blackwell, eds., 1986, Blackwell Scientific Publications).

This specification contains nucleotide and amino acid sequence information prepared using PatentIn Version 3.1, presented herein after the claims. Each nucleotide sequence is identified in the sequence listing by the numeric indicator <210> followed by the sequence identifier (e.g. <210>1, <210>2, <210>3, etc). The length and type of sequence (DNA, protein (PRT), etc), and source organism for each nucleotide sequence, are indicated by information provided in the numeric indicator fields <211>, <212> and <213>, respectively. Nucleotide sequences referred to in the specification are defined by the term "SEQ ID NO:", followed by the sequence identifier (eg. SEQ ID NO: 1 refers to the sequence in the sequence listing designated as <400>1).

The designation of nucleotide residues referred to herein are those recommended by the IUPAC-IUB Biochemical Nomenclature Commission, wherein A represents Adenine, C represents Cytosine, G represents Guanine, T represents thymine, Y represents a pyrimidine residue, R represents a purine residue, M represents Adenine or Cytosine, K represents Guanine or Thymine, S represents Guanine or Cytosine, W represents Adenine or Thymine, H represents a nucleotide other than Guanine, B represents a nucleotide other than Adenine, V represents a nucleotide other than Thymine, D represents a nucleotide other than Cytosine and N represents any nucleotide residue.

2. *Description of the related art*

Cancer is a multi-factorial disease and major cause of morbidity in humans and other animals, and deaths resulting from cancer in humans are increasing and expected to surpass deaths from heart disease in future. Carcinomas of the lung, prostate, breast, colon, pancreas, and ovary are major contributing factors to total cancer death in humans. For example, prostate cancer is the fourth most prevalent cancer and the second leading cause of cancer death in males. Similarly, cancer of the ovary is the second most common cancer of the female reproductive organs and the fourth most common cause of cancer death among females. With few exceptions, metastatic disease from carcinoma is fatal. Even if patients survive their primary cancers, recurrence or metastases are common.

It is widely recognized that simple and rapid tests for solid cancers or tumors have considerable clinical potential. Not only can such tests be used for the early diagnosis of

cancer but they also allow the detection of tumor recurrence following surgery and chemotherapy. A number of cancer-specific blood tests have been developed which depend upon the detection of tumor-specific antigens in the circulation (Catalona, W.J., *et al.*, 1991, "Measurement of prostate-specific antigen in serum as a screening test for prostate cancer", *N. Engl. J. Med.* 324, 1156-1161; Barrenetxea, G., *et al.*, 1998, "Use of serum tumor markers for the diagnosis and follow-up of breast cancer", *Oncology,* 55, 447-449; Cairns, P., and Sidreansky, D., 1999, "Molecular methods for the diagnosis of cancer". *Biochim. Biophys. Acta.* 1423, C 11-C 18).

Ovarian cancer is the fourth most frequent cause of cancer death in females and in the United States, and accounts for approximately 13,000 deaths annually. Furthermore, ovarian cancer remains the number one killer of women with gynaecological malignant hyperplasia and the incidence is rising in industrialized countries. The etiology of the neoplastic transformation remains unknown although there is epidemiological evidence for an association with disordered endocrine function. The incidence of ovarian carcinoma is higher in nulliparous females and in those with early menopause.

Most ovarian cancers are thought to arise from the ovarian surface of epithelium (OSE). Epithelial ovarian cancer is seldom encountered in women less than 35 years of age. Its incidence increases sharply with advancing age and peaks at ages 75 to 80, with the median age being 60 years. The single most important known risk factor is a strong familial history of breast or ovarian cancer. To date, little is known about the structure and function of the OSE cells. It is known that the OSE is highly dynamic tissue that undergoes morphogenic changes, and has proliferative properties sufficient to cover the ovulatory site following ovulation. Morphological and histochemical studies suggest that the OSE has secretory, endocytotic and transport functions which are hormonally-controlled (Blaustein and Lee, *Oncol. 8*, 34-43, 1979; Nicosia and Johnson, *Int. J. Gynecol. Pathol., 3*, 249-260, 1983; Papadaki and Beilby, *J. Cell Sci. 8,* 445-464, 1971; Anderson *et al., J. Morphol., 150*, 135-164, 1976).

Ovarian cancers are not readily detectable by diagnostic techniques (Siemens *et al., J. Cell. Physiol., 134*: 347-356, 1988). In fact, the diagnosis of carcinoma of the ovary is generally only possible when the disease has progressed to a late stage of development. Approximately 75% of women diagnosed with ovarian cancer are already at an advanced stage (III and IV) of the disease at their initial diagnosis. During the past 20 years, neither diagnosis nor five year survival rates have greatly improved for these patients. This is

substantially due to the high percentage of high-stage initial detection of the disease. There is therefore a need to develop new markers that improve early diagnosis and thereby reduce the percentage of high-stage initial diagnoses.

A number of proteinaceous ovarian tumor markers were evaluated several years ago, however these were found to be non-specific, and determined to be of low value as markers for primary ovarian cancer (Kudlacek *et al.*, *Gyn. Onc. 35*, 323-329, 1989; Rustin *et al.*, *J. Clin. Onc.*, *7*, 1667-1671, 1989; Sevelda *et al.*, *Am. J. Obstet. Gynecol.*, *161*, 1213-1216, 1989; Omar *et al.*, *Tumor Biol.*, *10*, 316-323, 1989). Several monoclonal antibodies were also shown to react with ovarian tumor associated antigens, however they were not specific for ovarian cancer and merely recognize determinants associated with high molecular weight mucin-like glycoproteins (Kenemans *et al.*, *Eur. J. Obstet. Gynecol. Repod. Biol. 29*, 207-218, 1989; McDuffy, *Ann. Clin. Biochem.*, *26*, 379-387, 1989). More recently, oncogenes associated with ovarian cancers have been identified, including *HER-2/neu* (*c-erbB-2*) which is over-expressed in one-third of ovarian cancers (USSN 6,075,122 by Cheever *et al*, issued June 13, 2000), the *fms* oncogene, and abnormalities in the *p53* gene, which are seen in about half of ovarian cancers.

Whilst previously identified markers for carcinomas of the ovary have facilitated efforts to diagnose and treat these serious diseases, there is a clear need for the identification of additional markers and therapeutic targets. The identification of tumor markers that are amenable to the early-stage detection of localized tumors is critical for more effective management of carcinomas of the ovary.

Summary of the invention

In work leading up to the present invention, the inventors sought to identify nucleic acid markers that were diagnostic of ovarian cancers generally, or diagnostic of specifc ovarian cancers such as, for example, serous ovarian cancer (SOC), mucinous ovarian cancer (MOC), non-invasive (borderline ovarian cancer or low malignant potential ovarian cancer), mixed phenotype ovarian cancer, endometrioid ovarian cancer (EnOC) and clear cell ovarian cancer (ClCA), papillary serous ovarian cancer, Brenner cell or undifferentiated adenocarcinoma, by virtue of their modulated expression in cancer tissues derived from a patient cohort compared to their expression in healthy or non-cancerous cells and tissues. Additionally, the inventors sought to determine whether any correlation exists between the expression of any particular gene in a subject having ovarian cancer and the survival, or likelihood for survivial, of the subject during the

medium to long term (i.e. in the period between about 1-2 years from primary diagnosis, or longer). The inventors also sought to to determine whether any correlation exists between the expression of any particular gene in a subject following treatment for ovarian cancer and the recurrence, or likelihood for recurrence, of ovarian cancer in the subject during the medium to long term (i.e. in the period between about 1-2 years from primary diagnosis, or longer).

As exemplified herein, the inventors identified a number of genes whose expression is altered (up-regulated or down-regulated) in individuals with ovarian cancer compared to healthy individuals., eg., subjects who do not have ovarian cancer. The particular genes are identified in Tables 1 and 2. Preferably, the genes are selected from the group of candidate genes set forth in Table 3.

The list of genes and proteins exemplified herein by Table 1 were identified by a statistical analysis as outlined in the examples which gave a P-value, eg., by comparison of expression to the expression of that gene in normal ovaries.

Accordingly, one aspect of the present invention provides a method of detecting an ovarian cancer-associated transcript in a biological sample, the method comprising contacting the biological sample with a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Table 1 or 2 or 3. Preferably the percentage identity to a sequence disclosed in any one of Tables 1-3 is at least about 85% or 90% or 95%, and still more preferably at least about 98% or 99%.

In a preferred embodiment, the present invention provides a method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein a modified level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has an ovarian cancer, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

(i) a sequence comprising at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 46, 48, 50, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;

(ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 46, 48, 50, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;

(iii) a sequence that is at least about 80% identical to a sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 46, 48, 50, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;

(iv) a sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 47, 49, 51, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82 and 84; and

(v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

In a preferred embodiment, the present invention provides a method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein a modified level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has an ovarian cancer, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

(i) a sequence comprising at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 46, 48, 50, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;

(ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 46, 48, 50, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;

(iii) a sequence that is at least about 80% identical to a sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27,

29, 31, 33, 35, 37, 39, 41, 43, 45, 46, 48, 50, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;

(iv) a sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 47, 49, 51, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82 and 84; and

(v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

Even more preferably, the present invention provides a method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein a modified level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has an ovarian cancer, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

(i) a sequence comprising at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 1, 5, 7, 9, 11, 13, 15, 17, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 45, 46, 48, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;

(ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 1, 5, 7, 9, 11, 13, 15, 17, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 45, 46, 48, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;

(iii) a sequence that is at least about 80% identical to a sequence selected from the group consisting of SEQ ID NOs: 1, 5, 7, 9, 11, 13, 15, 17, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 45, 46, 48, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;

(iv) a sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 6, 8, 10, 12, 14, 16, 18, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 47, 49, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82 and 84; and

(v) a sequence that is complementary to (i) or (ii) or (iii) or (iv).

As used herein, the term "modified level" includes an enhanced, increased or elevated level of an integer being assayed, or alternatively, a reduced or decreased level of an integer being assayed.

In one embodiment an elevated, enhanced or increased level of expression of the nucleic acid is detected. In accordance with this embodiment, the present invention provides a method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein an enhanced level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has an ovarian ovarian cancer, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

(i) a sequence comprising at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 or 2 other than a nucleic acid having an Accession Number selected from the group consisting of NM_022117, NM_005460, NM_002387, AI745249 and AI694200;

(ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 or 2 other than a nucleic acid having an Accession Number selected from the group consisting of NM_022117, NM_005460, NM_002387, AI745249 and AI694200;

(iii) a sequence that is at least about 80% identical to (i) or (ii);

(iv) a sequence that encodes a polypeptide encoded by a nucleic acid set forth in Table 1 or 2 other than a nucleic acid having an Accession Number selected from the group consisting of NM_022117, NM_005460, NM_002387, AI745249 and AI694200; and

(v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

In a preferred embodiment, the present invention provides a method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein an enhanced level of hybridization of the probe for the subject

being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has an ovarian cancer, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

(i) a sequence comprising at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 7, 9, 11, 13, 15, 17, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 45, 46, 48, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;

(ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 7, 9, 11, 13, 15, 17, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 45, 46, 48, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;

(iii) a sequence that is at least about 80% identical to a sequence selected from the group consisting of SEQ ID NOs: 7, 9, 11, 13, 15, 17, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 45, 46, 48, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;

(iv) a sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 10, 12, 14, 16, 18, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 47, 49, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82 and 84; and

(v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

In an alternative preferred embodiment, a reduced level of a diagnostic marker is indicative of ovarian cancer. In accordance with this embodiment, the present invention provides a method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein a reduced level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has an ovarian ovarian cancer, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

(i) a sequence comprising at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of NM_022117, NM_005460, NM_002387, AI745249 and AI694200;

(ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of NM_022117, NM_005460, NM_002387, AI745249 and AI694200;

(iii) a sequence that is at least about 80% identical to (i) or (ii);

(iv) a sequence that encodes a polypeptide encoded by a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of NM_022117, NM_005460, NM_002387, AI745249 and AI694200; and

(v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

In a preferred embodiment, the present invention provides a method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein a reduced level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has an ovarian cancer, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

(i) a sequence comprising at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 1, 3, and 5;

(ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 1, 3, and 5;

(iii) a sequence that is at least about 80% identical to a sequence selected from the group consisting of SEQ ID NOs: 1, 3, and 5;

(iv) a sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, and 6; and

(v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

Preferably, the ovarian cancer that is diagnosed according to the present invention is an epithelial ovarian cancer, such as, for example, serous ovarian cancer, non-invasive

ovarian cancer, mixed phenotpye ovarian cancer, mucinous ovarian cancer, endometrioid ovarian cancer, clear cell ovarian cancer, papillary serous ovarian cancer, Brenner cell or undifferentiated adenocarcinoma. As will be apparent from the preferred embodiments described below, certain of the genes represented in Table 1, Table 2 and Table 3 are expressed at modified levels in subjects having serous or mucinous ovarian cancers. Data presented in Figures 1-4 also exemplifiy novel diagnostics and prognostics for serous ovarian cancer, mucinous ovarian cancer, endometrioid ovarian cancer and clear cell ovarian cancer.

As exemplified herein by Table 2, the present inventors have identified those genes having an elevated or reduced average ratio of expression of specific genes between ovarian cancer patients vs non-ovarian cancer patients, wherein a high ratio in Table 2 indicates an enhanced expression in an ovarian cancer patients and wherein a negative ratio indicates that a reduced expression in an ovarian cancer patient.

In an alternative preferred embodiment, the present invention provides a method of diagnosing a serous ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein a modified level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has a serous ovarian cancer, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

(i) a sequence comprising at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 2 or as set forth in Table 1 and having an Accession Number selected from the group consisting of: U62801, D49441, X51630, and AB018305;

(ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 2 or as set forth in Table 1 and having an Accession Number selected from the group consisting of: U62801, D49441, X51630, And AB018305;

(iii) a sequence that is at least about 80% identical to (i) or (ii);

(iv) a sequence that encodes a polypeptide encoded by a nucleic acid set forth in Table 2 or as set forth in Table 1 and having an Accession Number selected from the group consisting of: U62801, D49441, X51630, And AB018305; and

(v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

In a further alternative preferred embodiment, the present invention provides a method of diagnosing a mucinous ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein an elevated level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has a mucinous ovarian cancer, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

(i) a sequence comprising at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: NM_006149, AA315933, U47732, NM_005588, AW503395, NM_004063, AI073913, AI928445, NM_022454, W40460, AA132961 and AF111856;

(ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: NM_006149, AA315933, U47732, NM_005588, AW503395, NM_004063, AI073913, AI928445, NM_022454, W40460, AA132961 and AF111856;

(iii) a sequence that is at least about 80% identical to (i) or (ii);

(iv) a sequence that encodes a polypeptide encoded by a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: NM_006149, AA315933, U47732, NM_005588, AW503395, NM_004063, AI073913, AI928445, NM_022454, W40460, AA132961 and AF111856; and

(v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

In a preferred embodiment, the present invention provides a method of diagnosing a mucinous ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein an enhanced level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not

having ovarian cancer indicates that the subject being tested has an ovarian cancer, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

(i) a sequence comprising at least about 20 contiguous nucleotides from SEQ ID NO: 57 or 59 or 61;

(ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from SEQ ID NO: 57 or 59 or 61;

(iii) a sequence that is at least about 80% identical to SEQ ID NO: 57 or 59 or 61;

(iv) a sequence that encodes the amino acid sequence set forth in SEQ ID NO: 58 or 60 or 62; and

(v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

Those skilled in the art will be aware that as a carcinoma progresses, metastases occur in organs and tissues outside the site of the primary tumor. For example, in the case of ovarian cancer, metastases commonly appear in a tissue selected from the group consisting of omentum, abdominal fluid, lymph nodes, lung, liver, brain, and bone. Accordingly, the term "ovarian cancer" as used herein shall be taken to include an early or developed tumor of the ovary, such as, for example, any one or more of a number of cancers of epithelial origin, such as serous, mucinous, endometrioid, clear cell, papillary serous, Brenner cell or undifferentiated adenocarcinoma, non-invasive ovarian cancer such as borderline ovarian cancer or low-malignant potential ovarian cancer, or a mixed phenotype ovarian cancer, and optionally, any metastases outside the ovary that occurs in a subject having a primary tumor of the ovary.

As used herein, the term "diagnosis", and variants thereof, such as, but not limited to "diagnose", "diagnosed" or "diagnosing" shall not be limited to a primary diagnosis of a clinical state, however should be taken to include any primary diagnosis or prognosis of a clinical state. For example, the "diagnostic assay" formats described herein are equally relevant to assessing the remission of a patient, or monitoring disease recurrence, or tumor recurrence, such as following surgery or chemotherapy, or determining the appearance of metastases of a primary tumor. All such uses of the assays described herein are encompassed by the present invention.

Both classical hybridization and amplification formats, and combinations thereof, are encompassed by the invention. In one embodiment, the hybridization comprises

performing a nucleic acid hybridization reaction between a labeled probe and a second nucleic acid in the biological sample from the subject being tested, and detecting the label. In another embodiment, the hybridization comprising performing a nucleic acid amplification reaction eg., polymerase chain reaction (PCR), wherein the probe consists of a nucleic acid primer and nucleic acid copies of the nucleic acid in the biological sample are amplified. As will be known to the skilled artisan, amplification may proceed classical nucleic acid hybridization detection systems, to enhance specificity of detection, particularly in the case of less abundant mRNA species in the sample.

In a preferred embodiment, the polynucleotide is immobilised on a solid surface.

The present invention clearly encompasses nucleic acid-based methods and protein-based methods for diagnosing cancer in humans and other mammals.

Accordingly, in a related embodiment, the present invention provides a method of detecting an ovarian cancer-associated polypeptide in a biological sample the method comprising contacting the biological sample with an antibody that binds specifically to an ovarian cancer-associated polypeptide in the biological sample, the polypeptide being encoded by a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-3.

Preferably the percentage identity to a sequence disclosed in any one of Tables 1-3 is at least about 85% or 90% or 95%, and still more preferably at least about 98% or 99%.

In a preferred embodiment, the present invention provides a method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein a modified level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer indicates that the subject being tested has an ovarian cancer, and wherein said antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a sequence having at least about 80% identity to a sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34,

36, 38, 40, 42, 44, 47, 49, 51, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82 and 84.

In a preferred embodiment, the present invention provides a method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein a modified level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer indicates that the subject being tested has an ovarian cancer, and wherein said antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a sequence having at least about 80% identity to a sequence selected from the group consisting of SEQ ID NOs: 2, 6, 8, 10, 12, 14, 16, 18, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 47, 49, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82 and 84.

In one embodiment an elevated, enhanced or increased level of expression of the antigen-antibody complex is detected. In accordance with this embodiment, the present invention provides a method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein an enhanced level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer indicates that the subject being tested has an ovarian cancer, and wherein said antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a polypeptide encoded by a nucleic acid set forth in Table 1 or 2 other than a nucleic acid having an Accession Number selected from the group consisting of NM_022117, NM_005460, NM_002387, AI745249 and AI694200.

In a preferred embodiment, the present invention provides a method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein an enhanced level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for

a control subject not having ovarian cancer indicates that the subject being tested has an ovarian cancer, and wherein said antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a sequence having at least about 80% identity to a sequence selected from the group consisting of SEQ ID NOs: 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 47, 49, 51, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82 and 84.

In an alternative preferred embodiment, a reduced level of a diagnostic marker is indicative of ovarian cancer. In accordance with this embodiment, the present invention provides a method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein a reduced level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer indicates that the subject being tested has an ovarian cancer, and wherein said antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a polypeptide encoded by a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of NM_022117, NM_005460, NM_002387, AI745249 and AI694200.

In a preferred embodiment, the present invention provides a method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein a reduced level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer indicates that the subject being tested has an ovarian cancer, and wherein said antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a sequence having at least about 80% identity to a sequence selected from the group consisting of SEQ ID NOs: 2, 4, and 6.

Preferably, the ovarian cancer that is diagnosed according to the present invention is an epithelial ovarian cancer, such as, for example, serous ovarian cancer or mucinous ovarian cancer.

In an alternative preferred embodiment, the present invention provides a method of diagnosing a serous ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein a modified level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer indicates that the subject being tested has a serous ovarian cancer, and wherein said antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a polypeptide encoded by a nucleic acid set forth in Table 2 or as set forth in Table 1 and having an Accession Number selected from the group consisting of: U62801, D49441, X51630, And AB018305.

In a further alternative preferred embodiment, the present invention provides a method of diagnosing a mucinous ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein a reduced level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer indicates that the subject being tested has a mucinous ovarian cancer, and wherein said antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a polypeptide encoded by a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: NM_006149, AA315933, U47732, NM_005588, AW503395, NM_004063, AI073913, AI928445, NM_022454, W40460, AA132961 and AF111856.

In a preferred embodiment, the present invention provides a method of diagnosing a mucinous ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein an enhanced level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer indicates that the subject being tested has a mucinous ovarian cancer, and wherein said antibody binds to a

polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a sequence having at least about 80% identity to SEQ ID NO: 58 or 60 or 62.

In a further related embodiment, the present invention provides a method of detecting an ovarian cancer-associated antibody in a biological sample the method comprising contacting the biological sample with a polypeptide encoded by a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-3, wherein the polypeptide specifically binds to the ovarian cancer-associated antibody.

Preferably, in the above methods, the biological sample is contacted with a plurality of the polynucleotides, polypeptides or antibodies referred to above.

In a particularly preferred embodiment, the present invention provides an antibody-based mulptiplex assay for determing the likelihood of survivial of a subject from an ovarian cancer. In one embodiment, the invention provides a method of determining the likelihood of survival of a subject suffering from a serous ovarian cancer, said method comprising contacting a biological sample from said subject being tested with at least two antibodies for a time and under conditions sufficient for antigen-antibody complexes to form and then detecting the complexes wherein an enhanced level of the antigen-antibody complexes for the subject being tested compared to the amount of the antigen-antibody complexes formed for a control subject not having ovarian cancer indicates that the subject being tested has a poor probability of survival, and wherein one antibody binds to an sFRP polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 72 and wherein one antibody binds to a SOCS3 polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 74.

The present invention is not to be limited by the source or nature of the biological sample. In one embodiment, the biological sample is from a patient undergoing a therapeutic regimen to treat ovarian cancer. In an alternative preferred embodiment, the biological sample is from a patient suspected of having ovarian cancer.

In addition to providing up-regulated and down-regulated genes, the list of genes and proteins exemplified herein by Table 1 were identified by a statistical analysis as outlined in the examples which gave a P-value, eg., by comparison of expression to

clinicopathological parameters for disease recurrence or patient survival. Accordingly, the present invention is particularly useful for prognostic applications, in particular for assessing the medium-to-long term survival of a subject having an ovarian cancer, or alternatively or in addition, for assessing the likelihood of disease recurrence.

Accordingly, a further aspect of the present invention provides a method of monitoring the efficacy of a therapeutic treatment of ovarian cancer, the method comprising:

(i) providing a biological sample from a patient undergoing the therapeutic treatment; and

(ii) determining the level of a ovarian cancer-associated transcript in the biological sample by contacting the biological sample with a polynucleotide that selectively hybridizes to a sequence having at least about 80% identity to a sequence as shown in any one of Tables 1-3, thereby monitoring the efficacy of the therapy.

Preferably the method further comprises comparing the level of the ovarian cancer-associated transcript to a level of the ovarian cancer-associated transcript in a biological sample from the patient prior to, or earlier in, the therapeutic treatment.

In a related embodiment, the present invention provides a method of monitoring the efficacy of a therapeutic treatment of ovarian cancer, the method comprising :

(i) providing a biological sample from a patient undergoing the therapeutic treatment; and

(ii) determining the level of a ovarian cancer-associated antibody in the biological sample by contacting the biological sample with a polypeptide encoded by a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-3, wherein the polypeptide specifically binds to the ovarian cancer-associated antibody, thereby monitoring the efficacy of the therapy.

Preferably the method further comprises comparing the level of the ovarian cancer-associated antibody to a level of the ovarian cancer-associated antibody in a biological sample from the patient prior to, or earlier in, the therapeutic treatment.

In a further related embodiment, the present invention provides a method of monitoring the efficacy of a therapeutic treatment of ovarian cancer, the method comprising :

(i) providing a biological sample from a patient undergoing the therapeutic treatment; and

(ii) determining the level of a ovarian cancer-associated polypeptide in the biological sample by contacting the biological sample with an antibody, wherein the antibody specifically binds to a polypeptide encoded by a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-3, thereby monitoring the efficacy of the therapy.

Preferably the method further comprises comparing the level of the ovarian cancer-associated polypeptide to a level of the ovarian cancer-associated polypeptide in a biological sample from the patient prior to, or earlier in, the therapeutic treatment.

It will also be apparent from the following preferred embodiments, that the expression of certain genes listed in Table 1 and Table 3 is statistically correlated with survival and death of patients having ovarian cancer, wherein a low P value indicates an enhanced likelihood that a patient having altered expression of the gene will die from the cancer.

Accordingly, in one embodiment, the present invention provides a method of determining the likelihood of survival of a subject suffering from an ovarian cancer, said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein an elevated level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has a poor probability of survival, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

(i) a sequence comprising at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: NM_003014, AA046217, NM_015902, T83882, AB040888, AA628980, AI623351, AW614420, AA243499, AF251237, AI970797, AF145713, X78565, T97307, BE243845, AW068302, AL133561, BE313555, X07820, AI973016, AF084545, U41518, Z11894, AW138190, BE086548, W47196, AI796870, X02761, AW968613, AW972565, AF045229, AW953853, U52426, F06700, AI798863, H52761, BE546947, AU076643, U20536, AA581602,

AJ245210, X65965, AI806770, BE386490, AW581992, U77534, AL034417, L10343, AW518944, W28729, AI640160, U11862, AW295980, X59135, BE466173, AI354722, M90464, AA829286, AI333771, BE465867, NM_014992, BE616902, AA430373, R27430, BE387335, AW264102, AW952323, AA088177, BE614567, AL079658, NM_002776, BE261944, NM_006379, AI002238, X81789, NM_002122, AB001914, AA311919, AI381750, AA292998, BE439580, AI677897, N72403, BE003054, AL035588, AI080491, AW770994, H24177, AF146761, NM_001955, AI680737, AI752666, AA505445, BE246649, and NM_003955;

(ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: NM_003014, AA046217, NM_015902, T83882, AB040888, AA628980, AI623351, AW614420, AA243499, AF251237, AI970797, AF145713, X78565, T97307, BE243845, AW068302, AL133561, BE313555, X07820, AI973016, AF084545, U41518, Z11894, AW138190, BE086548, W47196, AI796870, X02761, AW968613, AW972565, AF045229, AW953853, U52426, F06700, AI798863, H52761, BE546947, AU076643, U20536, AA581602, AJ245210, X65965, AI806770, BE386490, AW581992, U77534, AL034417, L10343, AW518944, W28729, AI640160, U11862, AW295980, X59135, BE466173, AI354722, M90464, AA829286, AI333771, BE465867, NM_014992, BE616902, AA430373, R27430, BE387335, AW264102, AW952323, AA088177, BE614567, AL079658, NM_002776, BE261944, NM_006379, AI002238, X81789, NM_002122, AB001914, AA311919, AI381750, AA292998, BE439580, AI677897, N72403, BE003054, AL035588, AI080491, AW770994, H24177, AF146761, NM_001955, AI680737, AI752666, AA505445, BE246649, and NM_003955;

(iii) a sequence that is at least about 80% identical to (i) or (ii);

(iv) a sequence that encodes a polypeptide encoded by a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: NM_003014, AA046217, NM_015902, T83882, AB040888, AA628980, AI623351, AW614420, AA243499, AF251237, AI970797, AF145713, X78565, T97307, BE243845, AW068302, AL133561, BE313555, X07820, AI973016, AF084545, U41518, Z11894, AW138190, BE086548, W47196, AI796870, X02761, AW968613, AW972565, AF045229, AW953853, U52426, F06700, AI798863, H52761, BE546947, AU076643, U20536, AA581602, AJ245210, X65965, AI806770, BE386490, AW581992, U77534, AL034417, L10343, AW518944, W28729, AI640160, U11862, AW295980, X59135, BE466173, AI354722,

M90464, AA829286, AI333771, BE465867, NM_014992, BE616902, AA430373, R27430, BE387335, AW264102, AW952323, AA088177, BE614567, AL079658, NM_002776, BE261944, NM_006379, AI002238, X81789, NM_002122, AB001914, AA311919, AI381750, AA292998, BE439580, AI677897, N72403, BE003054, AL035588, AI080491, AW770994, H24177, AF146761, NM_001955, AI680737, AI752666, AA505445, BE246649, and NM_003955; and

(v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

In a preferred embodiment, the present invention provides a method of determining the likelihood of survival of a subject suffering from an ovarian cancer, said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein an elevated level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has a poor probability of survival, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

(i) a sequence comprising at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;

(ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;

(iii) a sequence that is at least about 80% identical to a sequence selected from the group consisting of SEQ ID NOs: 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;

(iv) a sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NOs: 64, 66, 68, 70, 72, 74, 76, 78, 80, 82 and 84; and

(v) a sequence that is complementary to (i) or (ii) or (iii) or (iv).

In an alternative preferred embodiment, the present invention provides a method of determining the likelihood of survival of a subject suffering from an ovarian cancer, said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein an enhanced level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody

complex formed for a control subject not having ovarian cancer indicates that the subject being tested has has a poor probability of survival, and wherein said antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a sequence encoded by a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: NM_003014, AA046217, NM_015902, T83882, AB040888, AA628980, AI623351, AW614420, AA243499, AF251237, AI970797, AF145713, X78565, T97307, BE243845, AW068302, AL133561, BE313555, X07820, AI973016, AF084545, U41518, Z11894, AW138190, BE086548, W47196, AI796870, X02761, AW968613, AW972565, AF045229, AW953853, U52426, F06700, AI798863, H52761, BE546947, AU076643, U20536, AA581602, AJ245210, X65965, AI806770, BE386490, AW581992, U77534, AL034417, L10343, AW518944, W28729, AI640160, U11862, AW295980, X59135, BE466173, AI354722, M90464, AA829286, AI333771, BE465867, NM_014992, BE616902, AA430373, R27430, BE387335, AW264102, AW952323, AA088177, BE614567, AL079658, NM_002776, BE261944, NM_006379, AI002238, X81789, NM_002122, AB001914, AA311919, AI381750, AA292998, BE439580, AI677897, N72403, BE003054, AL035588, AI080491, AW770994, H24177, AF146761, NM_001955, AI680737, AI752666, AA505445, BE246649, and NM_003955.

In an alternative preferred embodiment, the present invention provides a method of determining the likelihood of survival of a subject suffering from an ovarian cancer, said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein an enhanced level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer indicates that the subject being tested has has a poor probability of survival, and wherein said antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a sequence having at least about 80% identity to a sequence selected from the group consisting of SEQ ID NOs: 64, 66, 68, 70, 72, 74, 76, 78, 80, 82 and 84.

In a particularly preferred embodiment, the present invention provides a marker for determining the likelihood of a subject surviving from serous cancer. In accordance with this embodiment of the invention, there is provided a method of determining the likelihood of survival of a subject suffering from a serous ovarian cancer, said method

comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein an elevated level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has a poor probability of survival, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

(i) a sequence comprising at least about 20 contiguous nucleotides from a nucleic acid comprising the nucleotide sequence set forth in SEQ ID NO: 71 or 73;
(ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a nucleic acid comprising the nucleotide sequence set forth in SEQ ID NO: 71 or 73;
(iii) a sequence that is at least about 80% identical to (i) or (ii) and encoding an sFRP protein or a SOCS3 protein;
(iv) a sequence that encodes a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 72 or 74; and
(v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

In an alternative preferred embodiment, the present invention provides a method of determining the likelihood of survival of a subject suffering from a serous ovarian cancer, said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein an enhanced level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer indicates that the subject being tested has a poor probability of survival, and wherein said antibody binds to an sFRP polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 72 or a SOCS3 polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 74 or.

It will also be apparent from the following preferred embodiments, that the expression of certain genes listed in Table 1 and Table 3 is statistically correlated with recurrence of ovarian cancer, wherein a low P value indicates an enhanced likelihood that a patient having altered expression of the gene will experience recurrence of the disease.

In yet another preferred embodiment, the present invention provides a method of determining the likelihood that a subject will suffer from a recurrence of an ovarian cancer, said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein an elevated level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has a high probability of recurrence, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

(i) a sequence comprising at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: M86849, AW963419, BE298665, AK000637, BE077546, T97307, R24601, BE090176, AA393907, W28729, BE313754, AW673081, AA356694, L08239, BE397649, NM_012317, NM_000947, AJ250562, AL040183, BE207573, BE564162, BE439580, AW067800, AA569756, AW138190, AF126245, L10343, NM_002514, AI863735, NM_005397, W26391, H15474, U51166, AA243499, AW408807, AI738719, AB040888, BE313077, AI677897, C14898, AI821730, AF007393, H65423, N46243, AA095971, U20350, NM_005756, D19589, AW957446, AW294647, BE159718, AI888490, AA022569, BE147740, AI798863, BE464341, AL080235, AI557212, X75208, AA628980, BE242587, NM_005512, AW953853, AU076611, AW968613, AL353944, BE614149, AA292998, H12912, AA188763, AK000596, AI970797, AW519204, Z42387, AF145713, AA972412, AK001564, AW959861, BE313555, W25005, AI193356, AF111106, AI130740, AA985190, BE221880, AF084545, R26584, AW247380, AA364261, U25849, AF262992, AW342140, AL133572, AI497778, AI745379, U51712, AW375974, AF251237, NM_000636, AA130986, AA216363, AA628980, AA811657, AA897108, AB040888, AF212225, AI089575, AI282028, AI368826, AI718702, AI827248, AK002039, AL109791, AW090198, AW296454, AW445034, AW452948, AW470411, AW885727, AW970859, AW979189, BE165866, BE175582, BE242587, BE271927, BE439580, BE464016, D63216, F34856, M83822, N33937, N49068, N51357, N80486, NM_000954, NM_005756, NM_016652, R26584, R31178, W05391, W25005, W45393, W68815, X65965, X76732 and Z45051,

(ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: M86849,

AW963419, BE298665, AK000637, BE077546, T97307, R24601, BE090176, AA393907, W28729, BE313754, AW673081, AA356694, L08239, BE397649, NM_012317, NM_000947, AJ250562, AL040183, BE207573, BE564162, BE439580, AW067800, AA569756, AW138190, AF126245, L10343, NM_002514, AI863735, NM_005397, W26391, H15474, U51166, AA243499, AW408807, AI738719, AB040888, BE313077, AI677897, C14898, AI821730, AF007393, H65423, N46243, AA095971, U20350, NM_005756, D19589, AW957446, AW294647, BE159718, AI888490, AA022569, BE147740, AI798863, BE464341, AL080235, AI557212, X75208, AA628980, BE242587, NM_005512, AW953853, AU076611, AW968613, AL353944, BE614149, AA292998, H12912, AA188763, AK000596, AI970797, AW519204, Z42387, AF145713, AA972412, AK001564, AW959861, BE313555, W25005, AI193356, AF111106, AI130740, AA985190, BE221880, AF084545, R26584, AW247380, AA364261, U25849, AF262992, AW342140, AL133572, AI497778, AI745379, U51712, AW375974, AF251237, NM_000636, AA130986, AA216363, AA628980, AA811657, AA897108, AB040888, AF212225, AI089575, AI282028, AI368826, AI718702, AI827248, AK002039, AL109791, AW090198, AW296454, AW445034, AW452948, AW470411, AW885727, AW970859, AW979189, BE165866, BE175582, BE242587, BE271927, BE439580, BE464016, D63216, F34856, M83822, N33937, N49068, N51357, N80486, NM_000954, NM_005756, NM_016652, R26584, R31178, W05391, W25005, W45393, W68815, X65965, X76732 and Z45051;

(iii) a sequence that is at least about 80% identical to (i) or (ii);

(iv) a sequence that encodes a polypeptide encoded by a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of:M86849, AW963419, BE298665, AK000637, BE077546, T97307, R24601, BE090176, AA393907, W28729, BE313754, AW673081, AA356694, L08239, BE397649, NM_012317, NM_000947, AJ250562, AL040183, BE207573, BE564162, BE439580, AW067800, AA569756, AW138190, AF126245, L10343, NM_002514, AI863735, NM_005397, W26391, H15474, U51166, AA243499, AW408807, AI738719, AB040888, BE313077, AI677897, C14898, AI821730, AF007393, H65423, N46243, AA095971, U20350, NM_005756, D19589, AW957446, AW294647, BE159718, AI888490, AA022569, BE147740, AI798863, BE464341, AL080235, AI557212, X75208, AA628980, BE242587, NM_005512, AW953853, AU076611, AW968613, AL353944, BE614149, AA292998, H12912, AA188763, AK000596, AI970797, AW519204, Z42387, AF145713, AA972412,

AK001564, AW959861, BE313555, W25005, AI193356, AF111106, AI130740, AA985190, BE221880, AF084545, R26584, AW247380, AA364261, U25849, AF262992, AW342140, AL133572, AI497778, AI745379, U51712, AW375974, AF251237, NM_000636, AA130986, AA216363, AA628980, AA811657, AA897108, AB040888, AF212225, AI089575, AI282028, AI368826, AI718702, AI827248, AK002039, AL109791, AW090198, AW296454, AW445034, AW452948, AW470411, AW885727, AW970859, AW979189, BE165866, BE175582, BE242587, BE271927, BE439580, BE464016, D63216, F34856, M83822, N33937, N49068, N51357, N80486, NM_000954, NM_005756, NM_016652, R26584, R31178, W05391, W25005, W45393, W68815, X65965, X76732 and Z45051; and

(v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

In an alternative preferred embodiment, the present invention provides a method of determining the likelihood that a subject will suffer from a recurrence of an ovarian cancer, said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein an enhanced level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer indicates that the subject being tested has a high probability of recurrence, and wherein said antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a sequence encoded by a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: M86849, AW963419, BE298665, AK000637, BE077546, T97307, R24601, BE090176, AA393907, W28729, BE313754, AW673081, AA356694, L08239, BE397649, NM_012317, NM_000947, AJ250562, AL040183, BE207573, BE564162, BE439580, AW067800, AA569756, AW138190, AF126245, L10343, NM_002514, AI863735, NM_005397, W26391, H15474, U51166, AA243499, AW408807, AI738719, AB040888, BE313077, AI677897, C14898, AI821730, AF007393, H65423, N46243, AA095971, U20350, NM_005756, D19589, AW957446, AW294647, BE159718, AI888490, AA022569, BE147740, AI798863, BE464341, AL080235, AI557212, X75208, AA628980, BE242587, NM_005512, AW953853, AU076611, AW968613, AL353944, BE614149, AA292998, H12912, AA188763, AK000596, AI970797, AW519204, Z42387, AF145713, AA972412, AK001564, AW959861, BE313555, W25005, AI193356,

AF111106, AI130740, AA985190, BE221880, AF084545, R26584, AW247380, AA364261, U25849, AF262992, AW342140, AL133572, AI497778, AI745379, U51712, AW375974, AF251237, NM_000636, AA130986, AA216363, AA628980, AA811657, AA897108, AB040888, AF212225, AI089575, AI282028, AI368826, AI718702, AI827248, AK002039, AL109791, AW090198, AW296454, AW445034, AW452948, AW470411, AW885727, AW970859, AW979189, BE165866, BE175582, BE242587, BE271927, BE439580, BE464016, D63216, F34856, M83822, N33937, N49068, N51357, N80486, NM_000954, NM_005756, NM_016652, R26584, R31178, W05391, W25005, W45393, W68815, X65965, X76732 and Z45051.

The recurrence of ovarian cancer is a clinical recurrence as determined by the presence of one or more clinical symptoms of an ovarian cancer, such as, for example, a metastases, or alternatively, as determined in a biochemical test, immunological test or serological test such as, for example, a cross-reactivity in a biological sample to a CA125 antibody.

Preferably, the recurrence is capable of being detected at least about 2 years from treatment, more preferably about 2-3 years from treatment, and even more preferably about 4 or 5 or 10 years from treatment.

Preferably, in the above diagnostic and/or prognostic methods, the biological sample is contacted with a plurality of the nucleic acids and/or polypeptides and/or antibodies referred to above. In a particularly preferred embodiment, mulpiplex assays are performed to detect enhanced expression at least of sFRP4 and SOC3 at the protein level (eg., using antigen-based or antibody-based assays) or at the mRNA level (eg., by detecting elevated levels of mRNA transcripts).

A further embodiment of the present invention provides a method of diagnosing epithelial ovarian cancer by detecting aberrant methylation of a promoter that regulates expression of a tumor suppressor gene eg., MCC. In particular, the present invention contemplates the detection of hypermethylation of the promoter of a tumor suppressor gene. Without being bound by any theory or mode of action, such hypermethylation leads to gene inactivation, thereby reducing expression fo the tumor suppressor gene and permitting oncogenesis. In one preferred embodiment, the present invention provides a method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising determining aberrant methylation in a promoter sequence that regulates

expression of a tumor suppressor gene in a biological sample from said subject compared to the methylation of the promoter in nucleic acid obtained for a control subject not having ovarian cancer wherein said aberrant methylation indicates that the subject being tested has an ovarian ovarian cancer.

In a further aspect, the present invention provides a method for identifying a compound that modulates an ovarian cancer-associated polypeptide, the method comprising :

(i) contacting the compound with a ovarian cancer-associated polypeptide, the polypeptide encoded by a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-3; and

(ii) determining the functional effect of the compound upon the polypeptide.

The functional effect may, for example, be a physical effect or a chemical effect. In one embodiment, the functional effect is determined by measuring ligand binding to the polypeptide. In a particular embodiment, the polypeptide is expressed in a eukaryotic host cell or cell membrane. Preferably the polypeptide is recombinant.

In another aspect, the present invention provides a method of inhibiting proliferation of a ovarian tumour cell, which method comprises contacting said cell with a compound identified using the method *supra* for identifying a compound that modulates an ovarian cancer-associated polypeptide.

In a further aspect, the present invention provides a method of inhibiting proliferation of a ovarian cancer-associated cell to treat ovarian cancer in a patient, the method comprising the step of administering to the patient a therapeutically effective amount of a compound identified using the method *supra* for identifying a compound that modulates an ovarian cancer-associated polypeptide.

In a further aspect, the present invention provides a drug screening assay comprising :

(i) administering a test compound to a mammal having ovarian cancer or a cell isolated therefrom;

(ii) comparing the level of gene expression of a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-3 in a treated cell or mammal with the level of gene expression of the polynucleotide in a control cell or mammal, wherein a test compound that

modulates the level of expression of the polynucleotide is a candidate for the treatment of ovarian cancer.

Typically, the control is a mammal with ovarian cancer or a cell therefrom that has not been treated with the test compound. Alternatively, the control is a normal cell or mammal.

The present invention also provides a method for treating a mammal having ovarian cancer comprising administering a compound identified the drug screening method *supra*.

In a further aspect, the present invention provides a pharmaceutical composition for use in treating a mammal having ovarian cancer, the composition comprising a compound identified the screening method *supra* for identifying a compound that modulates an ovarian cancer-associated polypeptide, or alternatively, using the drug screening method *supra*, and a physiologically acceptable carrier or diluent.

In a further aspect, the present invention provides an assay device, preferably for use in the diagnosis or prognosis of ovarian cancer, said device comprising a plurality of polynucleotides immobilized to a solid phase, wherein each of said polnucleotides consists of a gene as listed in any one of Tables 1-3. Preferably, the solid phase is a substantially planar chip.

In a related embodiment, the present invention provides an assay device, preferably for use in the diagnosis or prognosis of ovarian cancer, said device comprising a plurality of different antibodies immobilized to a solid phase, wherein each of said antibodies binds to a polypeptide listed in Tables 1-3. Preferably, the solid phase is a substantially planar chip.

Preferably, the assay device *supra* is used in a method of diagnosis or prognosis as described herein.

Alternatively, the assay device is used to identify modulatory compounds of the expression of one or more genes/proteins listed in any one of Tables 1-3.

In a further aspect, the present invention provides a non-human transgenic animal which is transgenic by virtue of comprising a gene set forth in any one of Tables 1-3 and, in particular, to the use of any such transgenic animal in the performance of a diagnostic or prognostic method of the invention as transgenic "knock-out" animals that have disrupted expression of a gene as set forth in any one of Tables 1-3.

In a further aspect, the present invention provides an isolated polynucleotide selected from the group consisting of:

(a) polynucleotides comprising a nucleotide sequence as shown in Tables 1-3, or the complement thereof;

(b) polynucleotides comprising a nucleotide sequence capable of selectively hybridizing to a nucleotide sequence as shown in Tables 1-3;

(c) polynucleotides comprising a nucleotide sequence capable of selectively hybridizing to the complement of a nucleotide sequence as shown in Tables 1-3; and

(d) polynucleotides comprising a polynucleotide sequence which is degenerate as a result of the genetic code to the polynucleotides defined in (a), (b) or (c).

Preferred polynucleotides comprise a polynucleotide sequence as shown in Tables 1-3 or a sequence having at least 80% homology thereto.

Preferably, the isolated polynucleotide is used for the diagnosis or prognosis of ovarian cancer, more preferably by a method as described herein. In a particularly preferred embodiment, the present invention provides for the use of a polynucleotide as set forth in any one of Tables 1-3 in the diagnosis or prognosis of ovarian cancer or for the preparation of a medicament for the treatment of ovarian cancer.

The present invention also provides a nucleic acid vector comprising a polynucleotide of the invention. In one embodiment, the polynucleotide is operably linked to a regulatory control sequence capable of directing expression of the polynucleotide in a host cell. In a particularly preferred embodiment, the present invention provides for the use of a vector comprising a polynucleotide as set forth in any one of Tables 1-3 in the diagnosis or prognosis of ovarian cancer or for the preparation of a medicament for the treatment of ovarian cancer.

The present invention further provides a host cell comprising a vector as described in the preceding paragraph. In a particularly preferred embodiment, the present invention provides for the use of a host cell comprising an introduced polynucleotide as set forth in any one of Tables 1-3 in the diagnosis or prognosis of ovarian cancer or for the preparation of a medicament for the treatment of ovarian cancer.

In a further aspect, the present invention provides an isolated polypeptide which is encoded by a gene set forth in any one of Tables 1-3. The present invention also provides an isolated polypeptide encoded by a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-3. In a particularly preferred embodiment, the present invention provides for the use of an isolated polypeptide as set forth in any one of Tables 1-3 in the diagnosis or prognosis of ovarian cancer or for the preparation of a medicament for the treatment of ovarian cancer.

In a further aspect the present invention provides an antibody that binds specifically a polypeptide listed in Tables 1-3. In a particularly preferred embodiment, the present invention provides for the use of an antibody that binds to an isolated polypeptide as set forth in any one of Tables 1-3 in the diagnosis or prognosis of ovarian cancer or for the preparation of a medicament for the treatment of ovarian cancer.

Brief description of the Drawings

Figure 1 is a photographic representation showing expression of genes as identified by immunohistochemical staining of fixed normal (i.e. non-cancerous or healthy) tissues (panel A) or ovarian cancer tissue (panel B). The inset in panel A shows inclusion cysts. The expression levels of the following genes listed in Table 1 or Table 3 were determined: Claudin-3 (SEQ ID NO: 15); EP-CAM (Accession No. NM_002354); and SOX17 (SEQ ID NO: 17). Positive controls CA125, MUC-1 and E-Cadherin were also included for comparison.

Figure 2 is a graphical representation showing the correlation between expression of different genes in serous ovarian cancer (SOC), mucinous ovarian cancer (MOC), endometroid ovarian cancer (EnOC) and clear cell ovarian cancer (ClCA). Genes indicated on the x-axis in each case are as in the legend to Figure 1.

Figure 3 is a copy of a photographic representation showing immunohistochemical staining of ovary tissue from a normal healthy subject (normal ovary), a subject diagnosed with mucinous ovarian cancer (MOC) and a subject diagnosed with serous ovarian cancer (SOC), following staining with probes that are specific for L1-Cadherin (top row), meprin alpha (middle row) or galectin-4 (lower row). Magnification is indicated as 20-40X.

Figure 4a is a copy of a photographic representation showing immunohistochemical staining of samples from a normal healthy subject (normal) or primary serous ovarian tumor (SOC), following staining with probes that are specific for sFRP4 (top row), or SOCS3 (lower row). Magnification is indicated as 20X.

Figure 4b is a copy of a graphical representation showing a Kaplan-Meier survival curve correlating sFRP4 expression to patient survival over the medium term (i.e., from about 12 months to about 48 months) to long term (more than about 48 months), indicating that high expression of sFRP4 is associated with poor survival in patients (n=127) having SOC (p=0.0056).

Detailed description of the preferred embodiments

Ovarian cancer-associated sequences

Ovarian cancer-associated sequences can include both nucleic acid (i.e., "ovarian cancer-associated genes") and protein (i.e., "ovarian cancer-associated proteins").

As used herein, the term "ovarian cancer-associated protein" shall be taken to mean any protein that has an expression pattern correlated to an ovarian cancer, the recurrence of an ovarian cancer or the survival of a subject suffering from ovarian cancer.

Similarly, the term "ovarian cancer-associated gene" shall be taken to mean any nucleic acid encoding an ovarian cancer-associated protein or nucleic acid having an expression profile that is correlated to an ovarian cancer, the recurrence of an ovarian cancer or the survival of a subject suffering from ovarian cancer.

As will be appreciated by those in the art and is more fully outlined below, ovarian cancer-associated genes are useful in a variety of applications, including diagnostic applications, which will detect naturally occurring nucleic acids, as well as screening applications; e.g., biochips comprising nucleic acid probes or PCR microtitre plates with selected probes to the ovarian cancer sequences are generated.

For identifying ovarian cancer-associated sequences, the ovarian cancer screen typically includes comparing genes identified in different tissues, e.g., normal and cancerous tissues, or tumour tissue samples from patients who have metastatic disease vs. non metastatic tissue. Other suitable tissue comparisons include comparing ovarian cancer samples with metastatic cancer samples from other cancers, such as lung, breast, gastrointestinal cancers, ovarian, etc. Samples of different stages of ovarian cancer, e.g., survivor tissue, drug resistant states, and tissue undergoing metastasis, are applied to biochips comprising nucleic acid probes. The samples are first microdissected, if applicable, and treated as is known in the art for the preparation of mRNA. Suitable biochips are commercially available, e.g. from Affymetrix. Gene expression profiles as described herein are generated and the data analyzed.

In one embodiment, the genes showing changes in expression as between normal and disease states are compared to genes expressed in other normal tissues, preferably normal ovarian, but also including, and not limited to lung, heart, brain, liver, breast, kidney, muscle, colon, small intestine, large intestine, spleen, bone and placenta. In a preferred embodiment, those genes identified during the ovarian cancer screen that are expressed in any significant amount in other tissues are removed from the profile, although in some embodiments, this is not necessary. That is, when screening for drugs, it is usually preferable that the target be disease specific, to minimise possible side effects.

In a preferred embodiment, ovarian cancer-associated sequences are those that are up-regulated in ovarian cancer; that is, the expression of these genes is modifed (up-

regulated or down-regulated) in ovarian cancer tissue as compared to non-cancerous tissue (see Table 1).

"Up-regulation" as used herein means at least about a two-fold change, preferably at least about a three fold change, with at least about five-fold or higher being preferred. All Unigene cluster identification numbers and accession numbers herein are for the GenBank sequence database and the sequences of the accession numbers are hereby expressly incorporated by reference. Sequences are also available in other databases, e.g., European Molecular Biology Laboratory (EMBL) and DNA Database of Japan (DDBJ).

"Down-regulation" as used herein often means at least about a 1.5-fold change more preferably a two-fold change, preferably at least about a three fold change, with at least about five-fold or higher being most preferred.

Particularly preferred sequences are those referred to in Tables 1 or 3 that have a P value of less than 0.05, more preferably a P value of less than about 0.01.

Similarly, preferred sequences are those referred to in Table 2 as having an absolute ratio of expression between ovarian patients and normal patients of at least about ±5.0, more preferably at least about ±6.0, even more preferrably at leat about ±7.0 or at least about ±8.0 or at least about ±9.0 or at least about ±10.0.

Detection of ovarian cancer sequences for diagnostic/prognostic applications

In one aspect, the RNA expression levels of genes are determined for different cellular states in the ovarian cancer phenotype. Expression levels of genes in normal tissue (i.e., not undergoing ovarian cancer) and in ovarian cancer tissue (and in some cases, for varying severities of ovarian cancer that relate to prognosis, as outlined below) are evaluated to provide expression profiles. An expression profile of a particular cell state or point of development is essentially a "fingerprint" of the state. While two states may have any particular gene similarly expressed, the evaluation of a number of genes simultaneously allows the generation of a gene expression profile that is reflective of the state of the cell. By comparing expression profiles of cells in different states, information regarding which genes are important (including both up- and down-regulation of genes) in each of these states is obtained. Then, diagnosis are performed or confirmed to

determine whether a tissue sample has the gene expression profile of normal or cancerous tissue. This will provide for molecular diagnosis of related conditions.

"Differential expression," or grammatical equivalents as used herein, refers to qualitative or quantitative differences in the temporal and/or cellular gene expression patterns within and among cells and tissue. Thus, a differentially expressed gene can qualitatively have its expression altered, including an activation or inactivation, in, e.g., normal versus ovarian cancer tissue. Genes are turned on or turned off in a particular state, relative to another state thus permitting comparison of two or more states. A qualitatively regulated gene will exhibit an expression pattern within a state or cell type which is detectable by standard techniques. Some genes will be expressed in one state or cell type, but not in both. Alternatively, the difference in expression are quantitative, e.g., in that expression is increased or decreased; i.e., gene expression is either upregulated, resulting in an increased amount of transcript, or downregulated, resulting in a decreased amount of transcript. The degree to which expression differs need only be large enough to quantify via standard characterization techniques as outlined below, such as by use of Affymetrix GeneChipTM expression arrays, Lockhart, *Nature Biotechnology 14:1675-1680 (1996),* hereby expressly incorporated by reference. Other techniques include, but are not limited to, quantitative reverse transcriptase PCR, northern analysis and RNase protection. As outlined above, preferably the change in expression (i.e., upregulation or downregulation) is at least about 50%, more preferably at least about 100%, more preferably at least about 150%, more preferably at least about 200%, with from 300 to at least 1000% being especially preferred.

Evaluation are at the gene transcript, or the protein level. The amount of gene expression are monitored using nucleic acid probes to the DNA or RNA equivalent of the gene transcript, and the quantification of gene expression levels, or, alternatively, the final gene product itself (protein) are monitored, e.g., with antibodies to the ovarian cancer-associated protein and standard immunoassays (ELISAs, etc.) or other techniques, including mass spectroscopy assays, 2D gel electrophoresis assays, etc. Proteins corresponding to ovarian cancer genes, i.e., those identified as being important in a ovarian cancer phenotype, are evaluated in a ovarian cancer diagnostic test.

In a preferred embodiment, gene expression monitoring is performed on a plurality of genes. Multiple protein expression monitoring are performed as well. Similarly, these assays are performed on an individual basis as well.

In this embodiment, the ovarian cancer nucleic acid probes are attached to biochips as outlined herein for the detection and quantification of ovarian cancer sequences in a particular cell. The assays are further described below in the example. PCR techniques are used to provide greater sensitivity.

In a preferred embodiment nucleic acids encoding the ovarian cancer-associated protein are detected. Although DNA or RNA encoding the ovarian cancer-associated protein are detected, of particular interest are methods wherein an mRNA encoding a ovarian cancer-associated protein is detected. Probes to detect mRNA are a nucleotide/deoxynucleotide probe that is complementary to and hybridizes with the mRNA and includes, but is not limited to, oligonucleotides, cDNA or RNA. Probes also should contain a detectable label, as defined herein. In one method the mRNA is detected after immobilizing the nucleic acid to be examined on a solid support such as nylon membranes and hybridizing the probe with the sample. Following washing to remove the non-specifically bound probe, the label is detected. In another method detection of the mRNA is performed in situ. In this method permeabilized cells or tissue samples are contacted with a detectably labeled nucleic acid probe for sufficient time to allow the probe to hybridize with the target mRNA. Following washing to remove the non-specifically bound probe, the label is detected. For example a digoxygenin labeled riboprobe (RNA probe) that is complementary to the mRNA encoding a ovarian cancer-associated protein is detected by binding the digoxygenin with an anti-digoxygenin secondary antibody and developed with nitro blue tetrazolium and 5-bromo-4-chloro-3-indoyl phosphate.

In a preferred embodiment, various proteins from the three classes of proteins as described herein (secreted, transmembrane or intracellular proteins) are used in diagnostic assays. The ovarian cancer-associated proteins, antibodies, nucleic acids, modified proteins and cells containing ovarian cancer sequences are used in diagnostic assays. This are performed on an individual gene or corresponding polypeptide level. In a preferred embodiment, the expression profiles are used, preferably in conjunction with high throughput screening techniques to allow monitoring for expression profile genes and/or corresponding polypeptides.

As described and defined herein, ovarian cancer-associated proteins, including intracellular, transmembrane or secreted proteins, find use as markers of ovarian cancer.

Detection of these proteins in putative ovarian cancer tissue allows for detection or diagnosis of ovarian cancer. In one embodiment, antibodies are used to detect ovarian cancer-associated proteins. A preferred method separates proteins from a sample by electrophoresis on a gel (typically a denaturing and reducing protein gel, but are another type of gel, including isoelectric focusing gels and the like). Following separation of proteins, the ovarian cancer-associated protein is detected, e.g., by immunoblotting with antibodies raised against the ovarian cancer-associated protein. Methods of immunoblotting are well known to those of ordinary skill in the art.

In another preferred method, antibodies to the ovarian cancer-associated protein find use in *in situ* imaging techniques, e.g., in histology (e.g., *Methods in Cell Biology: Antibodies in Cell* Biology, volume 37 (Asai, ed. 1993)). In this method cells are contacted with from one to many antibodies to the ovarian cancer-associated protein(s). Following washing to remove non-specific antibody binding, the presence of the antibody or antibodies is detected. In one embodiment the antibody is detected by incubating with a secondary antibody that contains a detectable label. In another method the primary antibody to the ovarian cancer-associated proteins) contains a detectable label, e.g. an enzyme marker that can act on a substrate. In another preferred embodiment each one of multiple primary antibodies contains a distinct and detectable label. This method finds particular use in simultaneous screening for a plurality of ovarian cancer-associated proteins. As will be appreciated by one of ordinary skill in the art, many other histological imaging techniques are also provided by the invention.

In a preferred embodiment the label is detected in a fluorometer which has the ability to detect and distinguish emissions of different wavelengths. In addition, a fluorescence activated cell sorter (FACS) are used in the method. In another preferred embodiment, antibodies find use in diagnosing ovarian cancer from blood, serum, plasma, stool, and other samples. Such samples, therefore, are useful as samples to be probed or tested for the presence of ovarian cancer-associated proteins. Antibodies are used to detect a ovarian cancer-associated protein by previously described immunoassay techniques including ELISA, immunoblotting (western blotting), immunoprecipitation, BIACORE technology and the like. Conversely, the presence of antibodies may indicate an immune response against an endogenous ovarian cancer-associated protein.

In a preferred embodiment, in situ hybridization of labeled ovarian cancer nucleic acid probes to tissue arrays is done. For example, arrays of tissue samples, including ovarian

cancer tissue and/or normal tissue, are made. In situ hybridization *(see, e.g.,* Ausubel, supra) is then performed. When comparing the fingerprints between an individual and a standard, the skilled artisan can make a diagnosis, a prognosis, or a prediction based on the findings. It is further understood that the genes which indicate the diagnosis may differ from those which indicate the prognosis and molecular profiling of the condition of the cells may lead to distinctions between responsive or refractory conditions or are predictive of outcomes.

In a preferred embodiment, the ovarian cancer-associated proteins, antibodies, nucleic acids, modified proteins and cells containing ovarian cancer sequences are used in prognosis assays. As above, gene expression profiles are generated that correlate to ovarian cancer, in terms of long term prognosis. Again, this are done on either a protein or gene level, with the use of genes being preferred. As above, ovarian cancer probes are attached to biochips for the detection and quantification of ovarian cancer sequences in a tissue or patient. The assays proceed as outlined above for diagnosis. PCR method may provide more sensitive and accurate quantification.

Characteristics of ovarian cancer-associated proteins and genes encoding same

Ovarian cancer-associated proteins of the present invention are classified as secreted proteins, transmembrane proteins or intracellular proteins. In one embodiment, the ovarian cancer-associated protein is an intracellular protein. Intracellular proteins are found in the cytoplasm and/or in the nucleus. Intracellular proteins are involved in all aspects of cellular function and replication (including, e.g., signaling pathways); aberrant expression of such proteins often results in unregulated or disregulated cellular processes *(see,* e.g., Molecular Biology of the Cell (Alberts, ed., 3rd ed., 1994). For example, many intracellular proteins have enzymatic activity such as protein kinase activity, protein phosphatase activity, protease activity, nucleotide cyclase activity, polymerase activity and the like. Intracellular proteins also serve as docking proteins that are involved in organizing complexes of proteins, or targeting proteins to various subcellular localizations, and are involved in maintaining the structural integrity of organelles.

An increasingly appreciated concept in characterising proteins is the presence in the proteins of one or more motifs for which defined functions have been attributed. In addition to the highly conserved sequences found in the enzymatic domain of proteins, highly conserved sequences have been identified in proteins that are involved in

protein-protein interaction. For example, Src-homology-2 (SH2) domains bind tyrosine-phosphorylated targets in a sequence dependent manner. PTB domains, which are distinct from SH2 domains, also bind tyrosine phosphorylated targets. SH3 domains bind to proline-rich targets. In addition, PH domains, tetratricopeptide repeats and WD domains to name only a few, have been shown to mediate protein-protein interactions. Some of these may also be involved in binding to phospholipids or other second messengers. As will be appreciated by one of ordinary skill in the art, these motifs are identified on the basis of primary sequence; thus, an analysis of the sequence of proteins may provide insight into both the enzymatic potential of the molecule and/or molecules with which the protein may associate. One useful database is Pfam (protein families), which is a large collection of multiple sequence alignments and hidden Markov models covering many common protein domains. Versions are available via the internet from Washington University in St. Louis, the Sanger Center in England, and the Karolinska Institute in Sweden *(see,* e.g., Bateman et al., 2000, Nuc. Acids Res. 28: 263-266; Sonnhammer et al., 1997, Proteins 28: 405-420; Bateman et al., 1999, Nuc. Acids Res. 27:260-262; and Sonnhammer et al., 1998, Nuc. Acids Res. 26: 320-322.

In another embodiment, the ovarian cancer sequences are transmembrane proteins. Transmembrane proteins are molecules that span a phospholipid bilayer of a cell. They may have an intracellular domain, an extracellular domain, or both. The intracellular domains of such proteins may have a number of functions including those already described for intracellular proteins. For example, the intracellular domain may have enzymatic activity and/or may serve as a binding site for additional proteins. Frequently the intracellular domain of transmembrane proteins serves both roles. For example certain receptor tyrosine kinases have both protein kinase activity and SH2 domains. In addition, autophosphorylation of tyrosines on the receptor molecule itself, creates binding sites for additional SH2 domain containing proteins.

Transmembrane proteins may contain from one to many transmembrane domains. For example, receptor tyrosine kinases, certain cytokine receptors, receptor guanylyl cyclases and receptor serine/threonine protein kinases contain a single transmembrane domain. However, various other proteins including channels and adenylyl cyclases contain numerous transmembrane domains. Many important cell surface receptors such as G protein coupled receptors (GPCRs) are classified as "seven transmembrane domain" proteins, as they contain 7 membrane spanning regions. Characteristics of transmembrane domains include approximately 20 consecutive hydrophobic amino acids

that are followed by charged amino acids. Therefore, upon analysis of the amino acid sequence of a particular protein, the localization and number of transmembrane domains within the protein are predicted *(see, e.g.* PSORT web site http://psort.nibb.ac.jp/). Important transmembrane protein receptors include, but are not limited to the insulin receptor, insulin-like growth factor receptor, human growth hormone receptor, glucose transporters, transferrin receptor, epidermal growth factor receptor, low density lipoprotein receptor, epidermal growth factor receptor, leptin receptor, interleukin receptors, e.g. IL-1 receptor, IL-2 receptor,

The extracellular domains of transmembrane proteins are diverse; however, conserved motifs are found repeatedly among various extracellular domains. Conserved structure and/or functions have been ascribed to different extracellular motifs. Many extracellular domains are involved in binding to other molecules. In one aspect, extracellular domains are found on receptors. Factors that bind the receptor domain include circulating ligands, which are peptides, proteins, or small molecules such as adenosine and the like. For example, growth factors such as EGF, FGF and PDGF are circulating growth factors that bind to their cognate receptors to initiate a variety of cellular responses. Other factors include cytokines, mitogenic factors, neurotrophic factors and the like. Extracellular domains also bind to cell-associated molecules. In this respect, they mediate cell-cell interactions., Cell-associated ligands are tethered to the cell, e.g., via a glycosylphosphatidylinositol (GPI) anchor, or may themselves be transmembrane proteins. Extracellular domains also associate with the extracellular matrix and contribute to the maintenance of the cell structure.

Ovarian cancer-associated proteins that are transmembrane are particularly preferred in the present invention as they are readily accessible targets for immunotherapeutics, as are described herein. In addition, as outlined below, transmembrane proteins are also useful in imaging modalities. Antibodies are used to label such readily accessible proteins *in situ*. Alternatively, antibodies can also label intracellular proteins, in which case samples are typically permeablized to provide access to intracellular proteins.

It will also be appreciated by those in the art that a transmembrane protein are made soluble by removing transmembrane sequences, e.g., through recombinant methods. Furthermore, transmembrane proteins that have been made soluble are made to be secreted through recombinant means by adding an appropriate signal sequence.

In another embodiment, the ovarian cancer-associated proteins are secreted proteins; the secretion of which are either constitutive or regulated. These proteins have a signal peptide or signal sequence that targets the molecule to the secretory pathway. Secreted proteins are involved in numerous physiological events; by virtue of their circulating nature, they serve to transmit signals to various other cell types. The secreted protein may function in an autocrine manner (acting on the cell that secreted the factor), a paracrine manner (acting on cells in close proximity to the cell that secreted the factor) or an endocrine manner (acting on cells at a distance). Thus secreted molecules find use in modulating or altering numerous aspects of physiology. Ovarian cancer-associated proteins that are secreted proteins are particularly preferred in the present invention as they serve as good targets for diagnostic markers, e.g., for blood, plasma, serum, or stool tests.

Mammalian subjects

The present invention provides nucleic acid and protein sequences that are differentially expressed in ovarian cancer, herein termed "ovarian cancer sequences." As outlined below, ovarian cancer sequences include those that are up-regulated (i.e., expressed at a higher level) in ovarian cancer, as well as those that are down-regulated (i.e., expressed at a lower level). In a preferred embodiment, the ovarian cancer sequences are from humans; however, as will be appreciated by those in the art, ovarian cancer sequences from other organisms are useful in animal models of disease and drug evaluation; thus, other ovarian cancer sequences are provided, from vertebrates, including mammals, including rodents (rats, mice, hamsters, guinea pigs, etc.), primates, farm animals (including sheep, goats, pigs, cows, horses, etc.) and pets, e.g., (dogs, cats, etc.).

Assay control samples

It will be apparent from the preceding discussion that many of the diagnostic methods provided by the present invention involve a degree of quantification to determine, on the one hand, the over-expression or reduced-expression of a diagnostic/prognostic marker in tissue that is suspected of comprising a cancer cell. Such quantification can be readily provided by the inclusion of appropriate control samples in the assays described below, derived from healthy or normal individuals. Alternatively, if internal controls are not included in each assay conducted, the control may be derived from an established data set that has been generated from healthy or normal individuals.

In the present context, the term "healthy individual" shall be taken to mean an individual who is known not to suffer from ovarian cancer, such knowledge being derived from clinical data on the individual, including, but not limited to, a different cancer assay to that described herein. As the present invention is particularly useful for the early detection of ovarian cancer, it is preferred that the healthy individual is asymptomatic with respect to the early symptoms associated with ovarian cancer. Although early detection using well-known procedures is difficult, reduced urinary frequency, rectal pressure, and abdominal bloating and swelling, are associated with the disease in its early stages, and, as a consequence, healthy individuals should not have any of these clinical symptoms. Clearly, subjects suffering from later symptoms associated with ovarian cancer, such as, for example, metastases in the omentum, abdominal fluid, lymph nodes, lung, liver, brain, or bone, and subjects suffering from spinal cord compression, elevated calcium level, chronic pain, or pleural effusion, should also be avoided from the "healthy individual" data set.

The term "normal individual" shall be taken to mean an individual having a normal level of expression of a cancer-associate gene or cancer-associated protein in a particular sample derived from said individual. As will be known to those skilled in the art, data obtained from a sufficiently large sample of the population will normalize, allowing the generation of a data set for determining the average level of a particular parameter. Accordingly, the level of expression of a cancer-associate gene or cancer-associated protein can be determined for any population of individuals, and for any sample derived from said individual, for subsequent comparison to levels determined for a sample being assayed. Where such normalized data sets are relied upon, internal controls are preferably included in each assay conducted to control for variation.

In one embodiment, the present invention provides a method for detecting a cancer cell in a subject, said method comprising:

(i) determining the level of mRNA encoding a cancer-associated protein expressed in a test sample from said subject; and

(ii) comparing the level of mRNA determined at (i) to the level of mRNA encoding a cancer-associated protein expressed in a comparable sample from a healthy or normal individual,

wherein a level of mRNA at (i) that is modified in the test sample relative to the comparable sample from the normal or healthy individual is indicative of the presence of a cancer cell in said subject.

Alternatively, or in addition, the controll may comprise a cancer-associated sequence that is known to be expressed at a particular level in an ovarian cancer, eg., CA125, MUC-1 or E-Cadherin, amongast others.

Biological samples

Preferred biological samples in which the assays of the invention are performed include bodily fluids, ovarian tissue and cells, and those tissues known to comprise cancer cells arising from a metastasis of an ovarian cancer, such as, for example, in carcinomas of the lung, prostate, breast, colon, pancreas, placenta, or omentum , and in cells of brain anaplastic oligodendrogliomas.

Bodily fluids shall be taken to include whole blood, serum, peripheral blood mononuclear cells (PBMC), or buffy coat fraction.

In the present context, the term "cancer cell" includes any biological specimen or sample comprising a cancer cell irrespective of its degree of isolation or purity, such as, for example, tissues, organs, cell lines, bodily fluids, or histology specimens that comprise a cell in the early stages of transformation or having been transformed.

As the present invention is particularly useful for the early detection and prognosis of cancer ofe rthe medium to long term, the definition of "cancer cell" is not to be limited by the stage of a cancer in the subject from which said cancer cell is derived (ie. whether or not the patient is in remission or undergoing disease recurrence or whether or not the cancer is a primary tumor or the consequence of metastases). Nor is the term "cancer cell" to be limited by the stage of the cell cycle of said cancer cell.

Preferably, the sample comprises ovarian tissue, prostate tissue, kidney tissue, uterine tissue, placenta, a cervical specimen, omentum, rectal tissue, brain tissue, bone tissue, lung tissue, lymphatic tissue, urine, semen, blood, abdominal fluid, or serum, or a cell preparation or nucleic acid preparation derived therefrom. More preferably, the sample comprises serum or abdominal fluid, or a tissue selected from the group consisting of: ovary, lymph, lung, liver, brain, placenta, brain, omentum, and prostate. Even more preferably, the sample comprises serum or abdominal fluid, ovary (eg. OSE), or lymph node tissue. The sample can be prepared on a solid matrix for histological analyses, or alternatively, in a suitable solution such as, for example, an extraction buffer or

suspension buffer, and the present invention clearly extends to the testing of biological solutions thus prepared.

Polynucleotide probes and amplification primers

Polynucleotide probes are derived from or comprise the nucleic acid sequences whose nucleotide sequences are provided by reference to the public database accession numbers given in Tables 1-3 (referred to herein as the nucleotide sequences shown in Tables 1-3), and sequences homologues thereto as well as variants, derivatives and fragments thereof.

Whilst the probes may comprise double-stranded or single-stranded nucleic acid, single-stranded probes are preferred because they do not require melting prior to use in hybridizations. On the other hand, longer probes are also preferred because they can be used at higher hybridization stringency than shorter probes and may produce lower background hybridization than shorter probes.

So far as shorter probes are concerned, single-stranded, chemically-synthesized oligonucleotide probes are particularly preferred by the present invention. To reduce the noise associated with the use of such probes during hybridization, the nucleotide sequence of the probe is carefully selected to maximize the Tm at which hybridizations can be performed, reduce non-specific hybridization, and to reduce self-hybridization. Such considerations may be particularly important for applications involving high throughput screening using microarray technology. In general, this means that the nucleotide sequence of an oligonucleotide probe is selected such that it is unique to the target RNA or protein-encoding sequence, has a low propensity to form secondary structure, low self-complementary, and is not highly A/T-rich.

The only requirement for the probes is that they cross-hybridize to nucleic acid encoding the target diagnostic protein or the complementary nucleotide sequence thereto and are sufficiently unique in sequence to generate high signal:noise ratios under specified hybridization conditions. As will be known to those skilled in the art, long nucleic acid probes are preferred because they tend to generate higher signal:noise ratios than shorter probes and/or the duplexes formed between longer molecules have higher melting temperatures (i.e. Tm values) than duplexes involving short probes. Accordingly, full-length DNA or RNA probes are contemplated by the present invention, as are specific probes comprising the sequence of the 3'-untranslated region or complementary thereto.

In a particularly preferred embodiment, the nucleotide sequence of an oligonucleotide probe has no detectable nucleotide sequence identity to a nucleotide sequence in a BLAST search (Altschul *et al., J. Mol. Biol. 215*, 403-410, 1990) or other database search, other than a sequence selected from the group consisting of: (a) a sequence encoding a polypeptide listed in any one of Tables 1-3; (b) the 5'-untranslated region of a sequence encoding a polypeptide listed in any one of Tables 1-3; (c) a 3'-untranslated region of a sequence encoding a polypeptide listed in any one of Tables 1-3; and (d) an exon region of a sequence encoding a polypeptide listed in any one of Tables 1-3.

Additionally, the self-complementarity of a nucleotide sequence can be determined by aligning the sequence with its reverse complement, wherein detectable regions of identity are indicative of potential self-complementarity. As will be known to those skilled in the art, such sequences may not necessarily form secondary structures during hybridization reaction, and, as a consequence, successfully identify a target nucleotide sequence. It is also known to those skilled in the art that, even where a sequence does form secondary structures during hybridization reactions, reaction conditions can be modified to reduce the adverse consequences of such structure formation. Accordingly, a potential for self-complementarity should not necessarily exclude a particular candidate oligonucleotide from selection. In cases where it is difficult to determine nucleotide sequences having no potential self-complementarity, the uniqueness of the sequence should outweigh a consideration of its potential for secondary structure formation.

Recommended pre-requisites for selecting oligonucleotide probes, particularly with respect to probes suitable for microarray technology, are described in detail by Lockhart *et al.*, "Expression monitoring by hybridization to high-density oligonucleotide arrays", *Nature Biotech.14*, 1675-1680, 1996.

The nucleic acid probe may comprise a nucleotide sequence that is within the coding strand of a gene listed in any one of Tables 1-3. Such "sense" probes are useful for detecting RNA by amplification procedures, such as, for example, polymerase chain reaction (PCR), and more preferably, quantitative PCR or reverse transcription polymerase chain reaction (RT-PCR). Alternatively, "sense" probes may be expressed to produce polypeptides or immunologically active derivatives thereof that are useful for detecting the expressed protein in samples.

The nucleotide sequences referred to in Tables 1-3 and homologues thereof, typically encode polypeptides. It will be understood by a skilled person that numerous different polynucleotides can encode the same polypeptide as a result of the degeneracy of the genetic code. In addition, it is to be understood that skilled persons may, using routine techniques, make nucleotide substitutions that do not affect the polypeptide sequence encoded by the polynucleotides of the invention to reflect the codon usage of any particular host organism in which the polypeptides of the invention are to be expressed.

Polynucleotides may comprise DNA or RNA. They are single-stranded or double-stranded. They may also be polynucleotides which include within them synthetic or modified nucleotides. A number of different types of modification to oligonucleotides are known in the art. These include methylphosphonate and phosphorothioate backbones, addition of acridine or polylysine chains at the 3' and/or 5' ends of the molecule. For the purposes of the present invention, it is to be understood that the polynucleotides described herein are modified by any method available in the art. Such modifications are carried out in order to enhance the *in vivo* activity or life span of the diagnostic/prognostic polynucleotides.

The terms "variant" or "derivative" in relation to the nucleotide sequences of the present invention include any substitution of, variation of, modification of, replacement of, deletion of or addition of one (or more) nucleic acid from or to the sequence provided that the resultant nucleotide sequence codes for a polypeptide having biological activity, preferably having substantially the same activity as the polypeptide sequences presented in the sequence listings.

With respect to sequence homology, preferably there is at least 75%, more preferably at least 85%, more preferably at least 90% homology to a sequence shown in Tables 1-3 herein over a region of at least 20, preferably at least 25 or 30, for instance at least 40, 60, 100, 500, 1000 or more contiguous nucleotides. More preferably there is at least 95%, more preferably at least 98%, homology. In one embodiment, homologues are naturally occurring sequences, such as orthologues, tissue-specific isoforms and allelic variants.

Homology comparisons are conducted by eye, or more usually, with the aid of readily available sequence comparison programs. These commercially available computer programs can calculate % homology between two or more sequences.

Percentage (%) homology are calculated over contiguous sequences, i.e. one sequence is aligned with the other sequence and each nucleotide in one sequence directly compared with the corresponding nucleotide in the other sequence, one base at a time. This is called an "ungapped" alignment. Typically, such ungapped alignments are performed only over a relatively short number of bases (for example less than 50 contiguous nucleotides).

Although this is a very simple and consistent method, it fails to take into consideration that, for example, in an otherwise identical pair of sequences, one insertion or deletion will cause the following nucleotides to be put out of alignment, thus potentially resulting in a large reduction in % homology when a global alignment is performed. Consequently, most sequence comparison methods are designed to produce optimal alignments that take into consideration possible insertions and deletions without penalising unduly the overall homology score. This is achieved by inserting "gaps" in the sequence alignment to try to maximise local homology.

However, these more complex methods assign "gap penalties" to each gap that occurs in the alignment so that, for the same number of identical amino acids, a sequence alignment with as few gaps as possible - reflecting higher relatedness between the two compared sequences - will achieve a higher score than one with many gaps. "Affine gap costs" are typically used that charge a relatively high cost for the existence of a gap and a smaller penalty for each subsequent residue in the gap. This is the most commonly used gap scoring system. High gap penalties will of course produce optimised alignments with fewer gaps. Most alignment programs allow the gap penalties to be modified. However, it is preferred to use the default values when using such software for sequence comparisons.

In determining whether or not two amino acid sequences fall within the stated defined percentage identity limits, those skilled in the art will be aware that it is necessary to conduct a side-by-side comparison of amino acid sequences. In such comparisons or alignments, differences will arise in the positioning of non-identical amino acid residues depending upon the algorithm used to perform the alignment. In the present context, references to percentage identities and similarities between two or more amino acid sequences shall be taken to refer to the number of identical and similar residues respectively, between said sequences as determined using any standard algorithm known to those skilled in the art. In particular, amino acid identities and similarities are calculated using the GAP program of the Computer Genetics Group, Inc., University

Research Park, Madison, Wisconsin, United States of America (Devereaux *et al*, *Nucl. Acids Res. 12,* 387-395,1984), which utilizes the algorithm of Needleman and Wunsch *J. Mol. Biol. 48,* 443-453, 1970, or alternatively, the CLUSTAL W algorithm of Thompson *et al., Nucl. Acids Res. 22,* 4673-4680, 1994, for multiple alignments, to maximize the number of identical/similar amino acids and to minimize the number and/or length of sequence gaps in the alignment.

A suitable computer program for carrying out such an alignment is the GCG Wisconsin Bestfit package (University of Wisconsin, U.S.A.; Devereux *et al.,* 1984, Nucleic Acids Research 12:387). The default scoring matrix has a match value of 10 for each identical nucleotide and -9 for each mismatch. The default gap creation penalty is -50 and the default gap extension penalty is -3 for each nucleotide.

Examples of other software than can perform sequence comparisons include, but are not limited to, the BLAST package (see Ausubel *et al.*, 1999 *ibid* – Chapter 18), FASTA (Atschul *et al.,* 1990, J. Mol. Biol., 403-410) and the GENEWORKS suite of comparison tools. Both BLAST and FASTA are available for offline and online searching (see Ausubel *et al.*, 1999 *ibid*, pages 7-58 to 7-60). However it is preferred to use the GCG Bestfit program.

Once the software has produced an optimal alignment, it is possible to calculate % homology, preferably % sequence identity. The software typically does this as part of the sequence comparison and generates a numerical result.

A preferred sequence comparison program is the GCG Wisconsin Bestfit program described above.

The present invention also encompasses the use of nucleotide sequences that are capable of hybridizing selectively to the sequences presented herein, or any variant, fragment or derivative thereof, or to the complement of any of the above. Nucleotide sequences are preferably at least 15 nucleotides in length, more preferably at least 20, 30, 40 or 50 nucleotides in length.

The term "hybridization" as used herein shall include "the process by which a strand of nucleic acid joins with a complementary strand through base pairing" as well as the process of amplification as carried out in polymerase chain reaction technologies.

Polynucleotides capable of selectively hybridizing to the nucleotide sequences presented herein, or to their complement, will be generally at least 70%, preferably at least 80 or 90% and more preferably at least 95% or 98% homologous to the corresponding nucleotide sequences referred to in Tables 1-3 over a region of at least 20, preferably at least 25 or 30, for instance at least 40, 60, 100, 500, 1000 or more contiguous nucleotides.

The term "selectively hybridizable" means that the polynucleotide used as a probe is used under conditions where a target polynucleotide is found to hybridize to the probe at a level significantly above background. The background hybridization may occur because of other polynucleotides present, for example, in the cDNA or genomic DNA library being screening. In this event, background implies a level of signal generated by interaction between the probe and a non-specific DNA member of the library which is less than 10 fold, preferably less than 100 fold as intense as the specific interaction observed with the target DNA. The intensity of interaction are measured, for example, by radiolabelling the probe, e.g. with ^{32}P.

Hybridization conditions are based on the melting temperature (Tm) of the nucleic acid binding complex, as taught in Berger and Kimmel (1987, Guide to Molecular Cloning Techniques, Methods in Enzymology, Vol 152, Academic Press, San Diego CA), and confer a defined "stringency" as explained below.

For the purposes of defining the level of stringency, a high stringency hybridization is achieved using a hybridization buffer and/or a wash solution comprising the following:

(i) a salt concentration that is equivalent to 0.1xSSC-0.2xSSC buffer or lower salt concentration;

(ii) a detergent concentration equivalent to 0.1% (w/v) SDS or higher; and

(iii) an incubation temperature of 55°C or higher.

Conditions for specifically hybridizing nucleic acid, and conditions for washing to remove non-specific hybridizing nucleic acid, are well understood by those skilled in the art. For the purposes of further clarification only, reference to the parameters affecting hybridization between nucleic acid molecules is found in Ausubel *et al.* (Current Protocols in Molecular Biology, Wiley Interscience, ISBN 047150338, 1992), which is herein incorporated by reference.

Maximum stringency typically occurs at about Tm-5°C (5°C below the Tm of the probe); high stringency at about 5°C to 10°C below Tm; intermediate stringency at about 10°C to 20°C below Tm; and low stringency at about 20°C to 25°C below Tm. As will be understood by those of skill in the art, a maximum stringency hybridization are used to identify or detect identical polynucleotide sequences while an intermediate (or low) stringency hybridization are used to identify or detect similar or related polynucleotide sequences.

In a preferred aspect, the present invention covers nucleotide sequences that can hybridize to the nucleotide sequence of the present invention under stringent conditions (e.g. 65°C and 0.1xSSC {1xSSC = 0.15 M NaCl, 0.015 M Na_3 Citrate pH 7.0}).

Where the diagnostic/prognostic polynucleotide is double-stranded, both strands of the duplex, either individually or in combination, are encompassed by the present invention. Where the polynucleotide is single-stranded, it is to be understood that the complementary sequence of that polynucleotide is also included within the scope of the present invention.

Polynucleotides which are not 100% homologous to the sequences of the present invention but are useful in perfoming the diagnostic and/or prognostic assays of the invetnion by virtue of their ability to selectively hybridize to the target gene transcript, or to encode an immunologically cross-reactive protein to the target protein, are obtained in a number of ways, such as, for example by probing DNA libraries made from a range of individuals, for example individuals from different populations. In particular, given that that changes in the expression of diagnostic/prognostic cancer-associated genes correlate with ovarian cancer, characterisation of variant sequences in individuals suffering from ovarian cancer is used to identify variations in the sequences of ovarian-cancer associated genes (and proteins) that are predictive of and/or causative of ovarian cancer.

Accordingly the present invention provides methods of identifying sequence variants that are associated with ovarian cancer which methods comprise determining all or part of the nucleotide sequence of a gene referred to in Tables 1-3, derived from an individual suffering from ovarian cancer and comparing the sequence to that of the corresponding wild-type gene.

In addition, other viral/bacterial, or cellular homologues particularly cellular homologues found in mammalian cells (e.g. rat, mouse, bovine and primate cells), are obtained and such

homologues and fragments thereof in general will be capable of selectively hybridizing to the sequences shown in the sequence listing herein. Such sequences are obtained by probing cDNA libraries made from or genomic DNA libraries from other animal species, and probing such libraries with probes comprising all or part of the sequences referred to in Tables 1-3 under conditions of medium to high stringency. Similar considerations apply to obtaining species homologues and allelic variants of the nucleotide sequences referred to in Tables 1-3.

Variants and strain/species homologues may also be obtained using degenerate PCR which will use primers designed to target sequences within the variants and homologues encoding conserved amino acid sequences within the sequences of the present invention. Conserved sequences are predicted, for example, by aligning the amino acid sequences from several variants/homologues. Sequence alignments are performed using computer software known in the art. For example the GCG Wisconsin PileUp program is widely used.

The primers used in degenerate PCR will contain one or more degenerate positions and will be used at stringency conditions lower than those used for cloning sequences with single sequence primers against known sequences.

Alternatively, such polynucleotides are obtained by site-directed mutagenesis of characterised sequences, such as the sequences referred to in Tables 1-3. This are useful where for example silent codon changes are required to sequences to optimise codon preferences for a particular host cell in which the polynucleotide sequences are being expressed. Other sequence changes are desired in order to introduce restriction enzyme recognition sites, or to alter the property or function of the polypeptides encoded by the polynucleotides..

Polynucleotides comprising a diagnostic/prognostic cancer-associated gene are used to produce a primer by standard derivatization means, e.g. a PCR primer, a primer for an alternative amplification reaction, a probe e.g. labelled with a detectable label by conventional means using radioactive or non-radioactive labels, or the polynucleotides are cloned into vectors. Such primers, probes and other fragments will be at least 15, preferably at least 20, for example at least 25, 30 or 40 nucleotides in length. Preferred fragments are less than 5000, 2000, 1000, 500 or 200 nucleotides in length.

Polynucleotides such as a DNA polynucleotides and probes according to the invention are produced by recombinant or synthetic means, including cloning by standard techniques.

In general, primers will be produced by synthetic means, involving a step wise manufacture of the desired nucleic acid sequence one nucleotide at a time. Techniques for accomplishing this using automated techniques are readily available in the art.

Longer polynucleotides will generally be produced using recombinant means, for example using PCR (polymerase chain reaction) cloning techniques. This will involve making a pair of primers (e.g. of about 15 to 30 nucleotides) flanking a region of the sequence which it is desired to clone, bringing the primers into contact with mRNA or cDNA obtained from an animal or human cell, performing a polymerase chain reaction under conditions which bring about amplification of the desired region, isolating the amplified fragment (e.g. by purifying the reaction mixture on an agarose gel) and recovering the amplified DNA. The primers are designed to contain suitable restriction enzyme recognition sites so that the amplified DNA are cloned into a suitable cloning vector

Polynucleotide probes or primers preferably carry a detectable label. Suitable labels include radioisotopes such as ^{32}P or ^{35}S, enzyme labels, or other protein labels such as biotin. Such labels are added to polynucleotides or primers and are detected using by techniques known in the art.

Polynucleotide probes or primers labeled or unlabeled are also used by a person skilled in the art in nucleic acid-based tests for detecting or sequencing diagnostic/prognostic cancer-associated gene.

Such tests for detecting generally comprise bringing a biological sample containing DNA or RNA into contact with a probe comprising a polynucleotide probe or primer under at least low stringency hybridization conditions and detecting any duplex formed between the probe/primer and nucleic acid in the sample. Such detection are achieved using techniques such as PCR or by immobilising the probe on a solid support, removing nucleic acid in the sample which is not hybridized to the probe, and then detecting nucleic acid which has hybridized to the probe. Alternatively, the sample nucleic acid are immobilised on a solid support, and the amount of probe bound to such a support are detected. Suitable assay methods of this and other formats are found in for example W089/03891 and W090/13667.

Tests for sequencing nucleotides include bringing a biological sample containing target DNA or RNA into contact with a probe comprising a polynucleotide probe or primer under at least low stringency hybridization conditions and determining the sequence by, for example the Sanger dideoxy chain termination method (see Sambrook et al.).

Such a method generally comprises elongating, in the presence of suitable reagents, the primer by synthesis of a strand complementary to the target DNA or RNA and selectively terminating the elongation reaction at one or more of an A, C, G or T/U residue; allowing strand elongation and termination reaction to occur; separating out according to size the elongated products to determine the sequence of the nucleotides at which selective termination has occurred. Suitable reagents include a DNA polymerase enzyme, the deoxynucleotides dATP, dCTP, dGTP and dTTP, a buffer and ATP. Dideoxynucleotides are used for selective termination.

Tests for detecting or sequencing nucleotides in a biological sample are used as part of the methods of the invention for detecting ovarian cancer-associated transcripts and monitoring the efficacy of treatment of patients suffering from ovarian cancer as described in more detail herein.

The probes/primers may conveniently be packaged in the form of a test kit in a suitable container. In such kits the probe are bound to a solid support where the assay format for which the kit is designed requires such binding. The kit may also contain suitable reagents for treating the sample to be probed, hybridizing the probe to nucleic acid in the sample, control reagents, instructions, and the like.

Preferably, a kit of the invention comprises primers/probes suitable for selectively detecting a plurality of sequences, more preferably for selectively detecting a plurality of sequences that are listed in one or more of Tables 1-3 as having a P value of less than 0.05, more preferably a P value of less than 0.01. Similarly, a kit of the invention preferably comprises primers suitable for selectively detecting a plurality of sequences referred to in Table 1 or 2 or 3.

Nucleic acid-based assay formats

As discussed in detail below, the status of expression of a cancer-associated gene in patient samples may be analyzed by a variety protocols that are well known in the art

including *in situ* hybridization, northern blotting techniques, RT-PCR analysis (such as, for example, performed on laser capture microdissected samples), and microarray technology, such as, for example, using tissue microarrays probed with nucleic acid probes, or nucleic acid microarrays (ie. RNA microarrays or amplified DNA microarrays) microarrays probed with nucleic acid probes. All such assay formats are encompassed by the present invention.

For high throughput screening of large numbers of samples, such as, for example, public health screening of subjects, particularly human subjects, having a higher risk of developing cancer, microarray technology is a preferred assay format.

In accordance with such high throughput formats, techniques for producing immobilised arrays of DNA molecules have been described in the art. Generally, most prior art methods describe how to synthesise single-stranded nucleic acid molecule arrays, using for example masking techniques to build up various permutations of sequences at the various discrete positions on the solid substrate. U.S. Patent No. 5,837,832, the contents of which are incorporated herein by reference, describes an improved method for producing DNA arrays immobilised to silicon substrates based on very large scale integration technology. In particular, U.S. Patent No. 5,837,832 describes a strategy called "tiling" to synthesize specific sets of probes at spatially-defined locations on a substrate which are used to produced the immobilised DNA arrays. U.S. Patent No. 5,837,832 also provides references for earlier techniques that may also be used.

Thus DNA are synthesised *in situ* on the surface of the substrate. However, DNA may also be printed directly onto the substrate using for example robotic devices equipped with either pins or piezo electric devices.

The plurality of polynucleotide sequences are typically immobilised onto or in discrete regions of a solid substrate. The substrate are porous to allow immobilisation within the substrate or substantially non-porous, in which case the library sequences are typically immobilised on the surface of the substrate. The solid substrate are made of any material to which polypeptides can bind, either directly or indirectly. Examples of suitable solid substrates include flat glass, silicon wafers, mica, ceramics and organic polymers such as plastics, including polystyrene and polymethacrylate. It may also be possible to use semi-permeable membranes such as nitrocellulose or nylon membranes, which are widely available. The semi-permeable membranes are mounted on a more robust solid

surface such as glass. The surfaces may optionally be coated with a layer of metal, such as gold, platinum or other transition metal. A particular example of a suitable solid substrate is the commercially available BIACore™ chip (Pharmacia Biosensors).

Preferably, the solid substrate is generally a material having a rigid or semi-rigid surface. In preferred embodiments, at least one surface of the substrate will be substantially flat, although in some embodiments it are desirable to physically separate synthesis regions for different polymers with, for example, raised regions or etched trenches. It is also preferred that the solid substrate is suitable for the high density application of DNA sequences in discrete areas of typically from 50 to 100 µm, giving a density of 10000 to 40000 cm^{-2}.

The solid substrate is conveniently divided up into sections. This are achieved by techniques such as photoetching, or by the application of hydrophobic inks, for example teflon-based inks (Cel-line, USA).

Discrete positions, in which each different member of the array is located may have any convenient shape, e.g., circular, rectangular, elliptical, wedge-shaped, etc.

Attachment of the polynucleotide sequences to the substrate are by covalent or non-covalent means. The plurality of polynucleotide sequences are attached to the substrate via a layer of molecules to which the sequences bind. For example, the sequences are labelled with biotin and the substrate coated with avidin and/or streptavidin. A convenient feature of using biotinylated sequences is that the efficiency of coupling to the solid substrate are determined easily. Since the library sequences may bind only poorly to some solid substrates, it is often necessary to provide a chemical interface between the solid substrate (such as in the case of glass) and the sequences. Examples of suitable chemical interfaces include hexaethylene glycol. Another example is the use of polylysine coated glass, the polylysine then being chemically modified using standard procedures to introduce an affinity ligand. Other methods for attaching molecules to the surfaces of solid substrate by the use of coupling agents are known in the art, see for example WO98/49557.

The complete DNA array is typically read at the same time by charged coupled device (CCD) camera or confocal imaging system. Alternatively, the DNA array are placed for detection in a suitable apparatus that can move in an x-y direction, such as a plate

reader. In this way, the change in characteristics for each discrete position are measured automatically by computer controlled movement of the array to place each discrete element in turn in line with the detection means.

The detection means are capable of interrogating each position in the library array optically or electrically. Examples of suitable detection means include CCD cameras or confocal imaging systems.

In a preferred embodiment, the level of expression of the cancer-associated gene in the test sample is determined by hybridizing a probe/primer to RNA in the test sample under at least low stringency hybridization conditions and detecting the hybridization using a detection means.

Similarly, the level of mRNA in the comparable sample from the healthy or normal individual is preferably determined by hybridizing a probe/primer to RNA in said comparable sample under at least low stringency hybridization conditions and detecting the hybridization using a detection means.

For the purposes of defining the level of stringency to be used in these diagnostic assays, a low stringency is defined herein as being a hybridization and/or a wash carried out in 6xSSC buffer, 0.1% (w/v) SDS at 28°C, or equivalent conditions. A moderate stringency is defined herein as being a hybridization and/or washing carried out in 2xSSC buffer, 0.1% (w/v) SDS at a temperature in the range 45°C to 65°C, or equivalent conditions. A high stringency is defined herein as being a hybridization and/or wash carried out in 0.1xSSC buffer, 0.1% (w/v) SDS, or lower salt concentration, and at a temperature of at least 65°C, or equivalent conditions. Reference herein to a particular level of stringency encompasses equivalent conditions using wash/hybridization solutions other than SSC known to those skilled in the art.

Generally, the stringency is increased by reducing the concentration of SSC buffer, and/or increasing the concentration of SDS and/or increasing the temperature of the hybridization and/or wash. Those skilled in the art will be aware that the conditions for hybridization and/or wash may vary depending upon the nature of the hybridization matrix used to support the sample RNA, or the type of hybridization probe used.

In general, the sample or the probe is immobilized on a solid matrix or surface (e.g., nitrocellulose). For high throughput screening, the sample or probe will generally comprise an array of nucleic acids on glass or other solid matrix, such as, for example, as described in WO 96/17958. Techniques for producing high density arrays are described, for example, by Fodor *et al.*, Science 767-773, 1991, and in U.S. Pat. No. 5,143,854. Typical protocols for other assay formats can be found, for example in Current Protocols In Molecular Biology, Unit 2 (Northern Blotting), Unit 4 (Southern Blotting), and Unit 18 (PCR Analysis), Frederick M. Ausubul *et al.* (ed)., 1995.

The detection means according to this aspect of the invention may be any nucleic acid-based detection means such as, for example, nucleic acid hybridization or amplification reaction (eg. PCR), a nucleic acid sequence-based amplification (NASBA) system, inverse polymerase chain reaction (iPCR), *in situ* polymerase chain reaction, or reverse transcription polymerase chain reaction (RT-PCR), amongst others.

The probe can be labelled with a reporter molecule capable of producing an identifiable signal (e.g., a radioisotope such as ^{32}P or ^{35}S, or a fluorescent or biotinylated molecule). According to this embodiment, those skilled in the art will be aware that the detection of said reporter molecule provides for identification of the probe and that, following the hybridization reaction, the detection of the corresponding nucleotide sequences in the sample is facilitated. Additional probes can be used to confirm the assay results obtained using a single probe.

Wherein the detection means is an amplification reaction such as, for example, a polymerase chain reaction or a nucleic acid sequence-based amplification (NASBA) system or a variant thereof, one or more nucleic acid probes molecules of at least about 20 contiguous nucleotides in length is hybridized to mRNA encoding a cancer-associated protein, or alternatively, hybridized to cDNA or cRNA produced from said mRNA, and nucleic acid copies of the template are enzymically-amplified.

Those skilled in the art will be aware that there must be a sufficiently high percentage of nucleotide sequence identity between the probes and the RNA sequences in the sample template molecule for hybridization to occur. As stated previously, the stringency conditions can be selected to promote hybridization.

In one format, PCR provides for the hybridization of non-complementary probes to different strands of a double-stranded nucleic acid template molecule (ie. a DNA/RNA, RNA/RNA or DNA/DNA template), such that the hybridized probes are positioned to facilitate the 5'-to 3' synthesis of nucleic acid in the intervening region, under the control of a thermostable DNA polymerase enzyme. In accordance with this embodiment, one sense probe and one antisense probe as described herein would be used to amplify DNA from the hybrid RNA/DNA template or cDNA.

In the present context, the cDNA would generally be produced by reverse transcription of mRNA present in the sample being tested (ie. RT-PCR). RT-PCR is particularly useful when it is desirable to determine expression of a cancer-associated gene. It is also known to those skilled in the art to use mRNA/DNA hybrid molecules as a template for such amplification reactions, and, as a consequence, first strand cDNA synthesis is all that is required to be performed prior to the amplification reaction.

Variations of the embodiments described herein are described in detail by McPherson *et al.,* PCR: A Practical Approach. (series eds, D. Rickwood and B.D. Hames), IRL Press Limited, Oxford. pp1-253, 1991.

The amplification reaction detection means described *supra* can be further coupled to a classical hybridization reaction detection means to further enhance sensitivity and specificity of the inventive method, such as by hybridizing the amplified DNA with a probe which is different from any of the probes used in the amplification reaction.

Similarly, the hybridization reaction detection means described *supra* can be further coupled to a second hybridization step employing a probe which is different from the probe used in the first hybridization reaction.

The comparison to be performed in accordance with the present invention may be a visual comparison of the signal generated by the probe, or alternatively, a comparison of data integrated from the signal, such as, for example, data that have been corrected or normalized to allow for variation between samples. Such comparisons can be readily performed by those skilled in the art.

Polypeptides

Cancer-associated polypeptides are encoded by cancer-associated genes. It will be understood that such polypeptides include those polypeptide and fragments thereof that are homologous to the polypeptides encoded by the nucleotide sequences referred to in Tables 1-3, which are obtained from any source, for example related viral/bacterial proteins, cellular homologues and synthetic peptides, as well as variants or derivatives thereof.

Thus, the present invention encompasses the use of variants, homologues or derivatives of the cancer-associated proteins described in the accompanying Tables. In one embodiment, homologues are naturally occurring sequences, such as orthologues, tissue-specific isoforms and allelic variants.

In the context of the present invention, a homologous sequence is taken to include an amino acid sequence which is at least 60, 70, 80 or 90% identical, preferably at least 95 or 98% identical at the amino acid level over at least 20, 40, 60 or 80 amino acids with a sequence encoded by a nucleotide sequence referred to in any one of Tables 1-3. In particular, homology should typically be considered with respect to those regions of the sequence known to be essential for specific biological functions rather than non-essential neighbouring sequences.

Although amino acid homology can also be considered in terms of similarity (i.e. amino acid residues having similar chemical properties/functions), in the context of the present invention it is preferred to express homology in terms of sequence identity.

Homology comparisons are carried out as described above for nucleotide sequences with the appropriate modifications for amino acid sequences. For example when using the GCG Wisconsin Bestfit package (see below) the default gap penalty for amino acid sequences is -12 for a gap and -4 for each extension.

It should also be noted that where computer algorithms are used to align amino acid sequences, although the final % homology are measured in terms of identity, the alignment process itself is typically not based on an all-or-nothing pair comparison. Instead, a scaled similarity score matrix is generally used that assigns scores to each pairwise comparison based on chemical similarity or evolutionary distance. An example

of such a matrix commonly used is the BLOSUM62 matrix - the default matrix for the BLAST suite of programs. GCG Wisconsin programs generally use either the public default values or a custom symbol comparison table if supplied (see user manual for further details). It is preferred to use the public default values for the GCG package, or in the case of other software, the default matrix, such as BLOSUM62.

The terms "variant" or "derivative" in relation to the amino acid sequences of the present invention includes any substitution of, variation of, modification of, replacement of, deletion of or addition of one (or more) amino acids from or to the sequence providing the resultant amino acid sequence preferably has biological activity, preferably having at least 25 to 50% of the activity as the polypeptides referred to in the sequence listings, more preferably at least substantially the same activity. Particular details of biological activity for each polypeptide are given in Tables 1-3.

Thus, the polypeptides referred to in Tables 1-3 and homologues thereof, are modified for use in the present invention. Typically, modifications are made that maintain the activity of the sequence. Thus, in one embodiment, amino acid substitutions are made, for example from 1, 2 or 3 to 10, 20 or 30 substitutions provided that the modified sequence retains at least about 25 to 50% of, or substantially the same activity. However, in an alternative preferred embodiment, modifications to the amino acid sequences of a cancer-associated protein are made intentionally to reduce the biological activity of the polypeptide. For example truncated polypeptides that remain capable of binding to target molecules but lack functional effector domains are useful as inhibitors of the biological activity of the full length molecule.

In general, preferably less than 20%, 10% or 5% of the amino acid residues of a variant or derivative are altered as compared with the corresponding region of the polypeptides referred to in Tables 1-3.

Amino acid substitutions may include the use of non-naturally occurring analogues, for example to increase blood plasma half-life of a therapeutically administered polypeptide (see below for further details on the production of peptide derivatives for use in therapy).

Conservative substitutions are made, for example according to the Table below. Amino acids in the same block in the second column and preferably in the same line in the third column are substituted for each other:

ALIPHATIC	Non-polar	G A P
		I L V
	Polar - uncharged	C S T M
		N Q
	Polar - charged	D E
		K R
AROMATIC		H F W Y

Cancer-associated proteins also include fragments of the above mentioned full length polypeptides and variants thereof, including fragments of the sequences referred to in Tables 1-3 and homologues thereof. Preferred fragments include those which include an epitope. Suitable fragments will be at least about 6 or 8, e.g. at least 10, 12, 15 or 20 amino acids in length. They may also be less than 200, 100 or 50 amino acids in length. Polypeptide fragments may contain one or more (e.g. 2, 3, 5, or 10) substitutions, deletions or insertions, including conserved substitutions. Where substitutions, deletion and/or insertions have been made, for example by means of recombinant technology, preferably less than 20%, 10% or 5% of the amino acid residues depicted in the sequence listings are altered.

Cancer-associated proteins are preferably in a substantially isolated form. It will be understood that the protein are mixed with carriers or diluents which will not interfere with the intended purpose of the protein and still be regarded as substantially isolated. A cancer-associated protein of the invention may also be in a substantially purified form, in which case it will generally comprise the protein in a preparation in which more than 90%, e.g. 95%, 98% or 99% pure as determined by SDS/PAGE or other art-recognized means for asessing protein purity.

Protein Production

For producing full-length polypeptides or immunologically active derivatives thereof by recombinant means, a protein-encoding region comprising at least about 15 contiguous nucleotides of the protein-encoding region of a nucleic acid referred to in any one of Tables 1-3 is placed in operable connection with a promoter or other regulatory sequence capable of regulating expression in a cell-free system or cellular system.

Reference herein to a "promoter" is to be taken in its broadest context and includes the transcriptional regulatory sequences of a classical genomic gene, including the TATA box which is required for accurate transcription initiation, with or without a CCAAT box sequence and additional regulatory elements (i.e., upstream activating sequences, enhancers and silencers) which alter gene expression in response to developmental and/or external stimuli, or in a tissue-specific manner. In the present context, the term "promoter" is also used to describe a recombinant, synthetic or fusion molecule, or derivative which confers, activates or enhances the expression of a nucleic acid molecule to which it is operably connected, and which encodes the polypeptide or peptide fragment. Preferred promoters can contain additional copies of one or more specific regulatory elements to further enhance expression and/or to alter the spatial expression and/or temporal expression of the said nucleic acid molecule.

Placing a nucleic acid molecule under the regulatory control of, i.e., "in operable connection with", a promoter sequence means positioning said molecule such that expression is controlled by the promoter sequence. Promoters are generally positioned 5' (upstream) to the coding sequence that they control. To construct heterologous promoter/structural gene combinations, it is generally preferred to position the promoter at a distance from the gene transcription start site that is approximately the same as the distance between that promoter and the gene it controls in its natural setting, i.e., the gene from which the promoter is derived. Furthermore, the regulatory elements comprising a promoter are usually positioned within 2 kb of the start site of transcription of the gene. As is known in the art, some variation in this distance can be accommodated without loss of promoter function. Similarly, the preferred positioning of a regulatory sequence element with respect to a heterologous gene to be placed under its control is defined by the positioning of the element in its natural setting, i.e., the genes from which it is derived. Again, as is known in the art, some variation in this distance can also occur.

The prerequisite for producing intact polypeptides and peptides in bacteria such as *E. coli* is the use of a strong promoter with an effective ribosome binding site. Typical promoters suitable for expression in bacterial cells such as *E. coli* include, but are not limited to, the *lacz* promoter, temperature-sensitive λ_L or λ_R promoters, T7 promoter or the IPTG-inducible *tac* promoter. A number of other vector systems for expressing the nucleic acid molecule of the invention in *E. coli* are well-known in the art and are described, for example, in Ausubel *et al* (*In:* Current Protocols in Molecular Biology. Wiley Interscience, ISBN 047150338, 1987) or Sambrook *et al* (*In:* Molecular cloning. A

laboratory manual, second edition, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., 1989). Numerous plasmids with suitable promoter sequences for expression in bacteria and efficient ribosome binding sites have been described, such as for example, pKC30 (λ_L: Shimatake and Rosenberg, *Nature 292*, 128, 1981); pKK173-3 (*tac*: Amann and Brosius, *Gene 40,* 183, 1985), pET-3 (T7: Studier and Moffat, *J. Mol. Biol. 189,* 113, 1986); the pBAD/TOPO or pBAD/Thio-TOPO series of vectors containing an arabinose-inducible promoter (Invitrogen, Carlsbad, CA), the latter of which is designed to also produce fusion proteins with thioredoxin to enhance solubility of the expressed protein; the pFLEX series of expression vectors (Pfizer Inc., CT, USA); or the pQE series of expression vectors (Qiagen, CA), amongst others.

Typical promoters suitable for expression in viruses of eukaryotic cells and eukaryotic cells include the SV40 late promoter, SV40 early promoter and cytomegalovirus (CMV) promoter, CMV IE (cytomegalovirus immediate early) promoter amongst others. Preferred vectors for expression in mammalian cells (eg. 293, COS, CHO, 293T cells) include, but are not limited to, the pcDNA vector suite supplied by Invitrogen, in particular pcDNA 3.1 myc-His-tag comprising the CMV promoter and encoding a C-terminal 6xHis and MYC tag; and the retrovirus vector pSRαtkneo (Muller *et al., Mol. Cell. Biol., 11*, 1785, 1991). The vector pcDNA 3.1 myc-His (Invitrogen) is particularly preferred for expressing a secreted form of a protein in 293T cells, wherein the expressed peptide or protein can be purified free of conspecific proteins, using standard affinity techniques that employ a Nickel column to bind the protein via the His tag.

A wide range of additional host/vector systems suitable for expressing polypeptides or immunological derivatives thereof are available publicly, and described, for example, in Sambrook *et al* (*In:* Molecular cloning. A laboratory manual, second edition, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., 1989).

Means for introducing the isolated nucleic acid molecule or a gene construct comprising same into a cell for expression are well-known to those skilled in the art. The technique used for a given organism depends on the known successful techniques. Means for introducing recombinant DNA into animal cells include microinjection, transfection mediated by DEAE-dextran, transfection mediated by liposomes such as by using lipofectamine (Gibco, MD, USA) and/or cellfectin (Gibco, MD, USA), PEG-mediated DNA uptake, electroporation and microparticle bombardment such as by using DNA-coated tungsten or gold particles (Agracetus Inc., WI, USA) amongst others.

For producing mutants, nucleotide insertion derivatives of the protein-encoding region are produced by making 5′ and 3′ terminal fusions, or by making intra-sequence insertions of single or multiple nucleotides or nucleotide analogues. Insertion nucleotide sequence variants are produced by introducing one or more nucleotides or nucleotide analogues into a predetermined site in the nucleotide sequence of said sequence, although random insertion is also possible with suitable screening of the resulting product being performed. Deletion variants are produced by removing one or more nucleotides from the nucleotide sequence. Substitutional nucleotide variants are produced by substituting at least one nucleotide in the sequence with a different nucleotide or a nucleotide analogue in its place, with the immunologically active derivative encoded therefor having an identical amino acid sequence , or only a limited number of amino acid modifications that do not alter its antigenicity compared to the base peptide or its ability to bind antibodies prepared against the base peptide. Such mutant derivatives will preferably have at least 80% identity with the base amino acid sequence from which they are derived.

Preferred immunologically active derivatives of a full-length polypeptide encoded by a gene referred to in any one of Tables 1-3 will comprise at least about 5-10 contiguous amino acids of the full-length amino acid sequence, more preferably at least about 10-20 contiguous amino acids in length, and even more preferably 20-30 contiguous amino acids in length.

For the purposes of producing derivatives using standard peptide synthesis techniques, such as, for example, Fmoc chemistry, a length not exceeding about 30-50 amino acids in length is preferred, as longer peptides are difficult to produce at high efficiency. Longer peptide fragments are readily achieved using recombinant DNA techniques wherein the peptide is expressed in a cell-free or cellular expression system comprising nucleic acid encoding the desired peptide fragment.

It will be apparent to the skilled artisan that any sufficiently antigenic region of at least about 5-10 amino acid residues can be used to prepare antibodies that bind generally to the polypeptides listed in Tables 1-3.

An expressed protein or synthetic peptide is preferably produced as a recombinant fusion protein, such as for example, to aid in extraction and purification. To produce a fusion

polypeptide, the open reading frames are covalently linked in the same reading frame, such as, for example, using standard cloning procedures as described by Ausubel *et al.* (Current Protocols in Molecular Biology, Wiley Interscience, ISBN 047150338, 1992), and expressed under control of a promoter. Examples of fusion protein partners include glutathione-S-transferase (GST), FLAG, hexahistidine, GAL4 (DNA binding and/or transcriptional activation domains) and β-galactosidase. It may also be convenient to include a proteolytic cleavage site between the fusion protein partner and the protein sequence of interest to allow removal of fusion protein sequences. Preferably the fusion protein will not hinder the immune function of the target protein.

In a particularly preferred embodiment, polypeptides are produced substantially free of conspecific proteins. Such purity can be assessed by standard procedures, such as, for example, SDS/polyacrylamide gel electrophoresis, 2-dimensional gene electrophoresis, chromatography, amino acid composition analysis, or amino acid sequence analysis.

To produce isolated polypeptides or fragments, eg., for antibody production, standard protein purification techniques may be employed. For example, gel filtration, ion exchange chromatography, reverse phase chromatography, or affinity chromatography, or a combination of any one or more said procedures, may be used. High pressure and low pressure procedures can also be employed, such as, for example, FPLC, or HPLC. To isolate the full-length proteins or peptide fragments comprising more than about 50-100 amino acids in length, it is particularly preferred to express the polypeptide in a suitable cellular expression system in combination with a suitable affinity tag, such as a 6xHis tag, and to purify the polypeptide using an affinity step that bonds it via the tag (*supra*). Optionally, the tag may then be cleaved from the expressed polypeptide.

Alternatively, for short immunologically active derivatives of a full-length polypeptide, preferably those peptide fragments comprising less than about 50 amino acids in length, chemical synthesis techniques are conveniently used. As will be known to those skilled in the art, such techniques may also produce contaminating peptides that are shorter than the desired peptide, in which case the desired peptide is conveniently purified using reverse phase and/or ion exchange chromatography procedures at high pressure (ie. HPLC or FPLC).

Antibodies

The invention also provides monoclonal or polyclonal antibodies that bind specifically to polypeptides of the invention or fragments thereof. Thus, the present invention further provides a process for the production of monoclonal or polyclonal antibodies to polypeptides of the invention.

The phrase "binds specifically" to a polypeptide means that the binding of the antibody to the protein or peptide is determinative of the presence of the protein, in a heterogeneous population of proteins and other biologics. Thus, under designated immunoassay conditions, the specified antibodies bind to a particular protein at least two times the background and more typically more than 10 to 100 times background. Typically, antibodies of the invention bind to a protein of interest with a Kd of at least about 0.1 mM, more usually at least about 1 μM, preferably at least about 0.1 μM, and most preferably at least, 0.01 μM.

Reference herein to antibody or antibodies includes whole polyclonal and monoclonal antibodies, and parts thereof, either alone or conjugated with other moieties. Antibody parts include Fab and $F(ab)_2$ fragments and single chain antibodies. The antibodies may be made *in vivo* in suitable laboratory animals, or, in the case of engineered antibodies (Single Chain Antibodies or SCABS, etc) using recombinant DNA techniques *in vitro.*

In accordance with this aspect of the invention, the antibodies may be produced for the purposes of immunizing the subject, in which case high titer or neutralizing antibodies that bind to a B cell epitope will be especially preferred. Suitable subjects for immunization will, of course, depend upon the immunizing antigen or antigenic B cell epitope. It is contemplated that the present invention will be broadly applicable to the immunization of a wide range of animals, such as, for example, farm animals (e.g. horses, cattle, sheep, pigs, goats, chickens, ducks, turkeys, and the like), laboratory animals (e.g. rats, mice, guinea pigs, rabbits), domestic animals (cats, dogs, birds and the like), feral or wild exotic animals (e.g. possums, cats, pigs, buffalo, wild dogs and the like) and humans.

Alternatively, the antibodies may be for commercial or diagnostic purposes, in which case the subject to whom the diagnostic/prognostic protein or immunogenic fragment or epitope thereof is administered will most likely be a laboratory or farm animal. A wide range of animal species are used for the production of antisera. Typically the animal used for production of antisera is a rabbit, a mouse, rat, hamster, guinea pig, goat,

sheep, pig, dog, horse, or chicken. Because of the relatively large blood volume of rabbits, a rabbit is a preferred choice for production of polyclonal antibodies. However, as will be known to those skilled in the art, larger amounts of immunogen are required to obtain high antibodies from large animals as opposed to smaller animals such as mice. In such cases, it will be desirable to isolate the antibody from the immunized animal.

Preferably, the antibody is a high titer antibody. By "high titer" means a sufficiently high titer to be suitable for use in diagnostic or therapeutic applications. As will be known in the art, there is some variation in what might be considered "high titer". For most applications a titer of at least about 10^3-10^4 is preferred. More preferably, the antibody titer will be in the range from about 10^4 to about 10^5 , even more preferably in the range from about 10^5 to about 10^6.

More preferably, in the case of B cell epitopes from pathogens, viruses or bacteria, the antibody is a neutralizing antibody (i.e. it is capable of neutralizing the infectivity of the organism fro which the B cell epitope is derived).

To generate antibodies, the diagnostic/prognostic protein or immunogenic fragment or epitope thereof, optionally formulated with any suitable or desired carrier, adjuvant, BRM, or pharmaceutically acceptable excipient, is conveniently administered in the form of an injectable composition. Injection may be intranasal, intramuscular, sub-cutaneous, intravenous, intradermal, intraperitoneal, or by other known route. For intravenous injection, it is desirable to include one or more fluid and nutrient replenishers. Means for preparing and characterizing antibodies are well known in the art. (See, e.g., ANTIBODIES: A LABORATORY MANUAL, Cold Spring Harbor Laboratory, 1988, incorporated herein by reference).

The efficacy of the diagnostic/prognostic protein or immunogenic fragment or epitope thereof in producing an antibody is established by injecting an animal, for example, a mouse, rat, rabbit, guinea pig, dog, horse, cow, goat or pig, with a formulation comprising the diagnostic/prognostic protein or immunogenic fragment or epitope thereof, and then monitoring the immune response to the B cell epitope, as described in the Examples. Both primary and secondary immune responses are monitored. The antibody titer is determined using any conventional immunoassay, such as, for example, ELISA, or radio immunoassay.

The production of polyclonal antibodies may be monitored by sampling blood of the immunized animal at various points following immunization. A second, booster injection, may be given, if required to achieve a desired antibody titer. The process of boosting and titering is repeated until a suitable titer is achieved. When a desired level of immunogenicity is obtained, the immunized animal is bled and the serum isolated and stored, and/or the animal is used to generate monoclonal antibodies (Mabs).

For the production of monoclonal antibodies (Mabs) any one of a number of well-known techniques may be used, such as, for example, the procedure exemplified in US Patent No. 4,196,265, incorporated herein by reference.

For example, a suitable animal will be immunized with an effective amount of the diagnostic/prognostic protein or immunogenic fragment or epitope thereof under conditions sufficient to stimulate antibody producing cells. Rodents such as mice and rats are preferred animals, however, the use of rabbit, sheep, or frog cells is also possible. The use of rats may provide certain advantages, but mice are preferred, with the BALB/c mouse being most preferred as the most routinely used animal and one that generally gives a higher percentage of stable fusions.

Following immunization, somatic cells with the potential for producing antibodies, specifically B lymphocytes (B cells), are selected for use in the MAb generating protocol. These cells may be obtained from biopsied spleens, tonsils or lymph nodes, or from a peripheral blood sample. Spleen cells and peripheral blood cells are preferred, the former because they are a rich source of antibody-producing cells that are in the dividing plasmablast stage, and the latter because peripheral blood is easily accessible. Often, a panel of animals will have been immunized and the spleen of animal with the highest antibody titer removed. Spleen lymphocytes are obtained by homogenizing the spleen with a syringe. Typically, a spleen from an immunized mouse contains approximately 5 x 10^7 to 2 x 10^8 lymphocytes.

The B cells from the immunized animal are then fused with cells of an immortal myeloma cell, generally derived from the same species as the animal that was immunized with the diagnostic/prognostic protein or immunogenic fragment or epitope thereof. Myeloma cell lines suited for use in hybridoma-producing fusion procedures preferably are non-antibody-producing, have high fusion efficiency and enzyme deficiencies that render them incapable of growing in certain selective media which support the growth of only the

desired fused cells, or hybridomas. Any one of a number of myeloma cells may be used and these are known to those of skill in the art (e.g. murine P3-X63/Ag8, X63-Ag8.653, NS1/1.Ag 4 1, Sp210-Ag14, FO, NSO/U, MPC-11, MPC11-X45-GTG 1.7 and S194/5XX0; or rat R210.RCY3, Y3-Ag 1.2.3, IR983F and 4B210; and U-266, GM1500-GRG2, LICR-LON-HMy2 and UC729-6). A preferred murine myeloma cell is the NS-1 myeloma cell line (also termed P3-NS-1-Ag4-1), which is readily available from the NIGMS Human Genetic Mutant Cell Repository under Accession No. GM3573. Alternatively, a murine myeloma SP2/0 non-producer cell line that is 8-azaguanine-resistant is used.

To generate hybrids of antibody-producing spleen or lymph node cells and myeloma cells, somatic cells are mixed with myeloma cells in a proportion between about 20:1 to about 1:1, respectively, in the presence of an agent or agents (chemical or electrical) that promote the fusion of cell membranes. Fusion methods using Sendai virus have been described by Kohler and Milstein, *Nature 256*, 495-497, 1975; and Kohler and Milstein, *Eur. J. Immunol. 6*, 511-519, 1976. Methods using polyethylene glycol (PEG), such as 37% (v/v) PEG, are described in detail by Gefter *et al., Somatic Cell Genet. 3,* 231-236, 1977. The use of electrically induced fusion methods is also appropriate.

Hybrids are amplified by culture in a selective medium comprising an agent that blocks the *de novo* synthesis of nucleotides in the tissue culture media. Exemplary and preferred agents are aminopterin, methotrexate and azaserine. Aminopterin and methotrexate block de novo synthesis of both purines and pyrimidines, whereas azaserine blocks only purine synthesis. Where aminopterin or methotrexate is used, the media is supplemented with hypoxanthine and thymidine as a source of nucleotides (HAT medium). Where azaserine is used, the media is supplemented with hypoxanthine.

The preferred selection medium is HAT, because only those hybridomas capable of operating nucleotide salvage pathways are able to survive in HAT medium, whereas myeloma cells are defective in key enzymes of the salvage pathway, (e.g., hypoxanthine phosphoribosyl transferase or HPRT), and they cannot survive. B cells can operate this salvage pathway, but they have a limited life span in culture and generally die within about two weeks. Accordingly, the only cells that can survive in the selective media are those hybrids formed from myeloma and B cells.

The amplified hybridomas are subjected to a functional selection for antibody specificity and/or titer, such as, for example, by immunoassay (e.g. radioimmunoassay, enzyme immunoassay, cytotoxicity assay, plaque assay, dot immunobinding assay, and the like).

The selected hybridomas are serially diluted and cloned into individual antibody-producing cell lines, which clones can then be propagated indefinitely to provide MAbs. The cell lines may be exploited for MAb production in two basic ways. A sample of the hybridoma is injected, usually in the peritoneal cavity, into a histocompatible animal of the type that was used to provide the somatic and myeloma cells for the original fusion. The injected animal develops tumors secreting the specific monoclonal antibody produced by the fused cell hybrid. The body fluids of the animal, such as serum or ascites fluid, can then be tapped to provide MAbs in high concentration. The individual cell lines could also be cultured *in vitro*, where the MAbs are naturally secreted into the culture medium from which they are readily obtained in high concentrations. MAbs produced by either means may be further purified, if desired, using filtration, centrifugation and various chromatographic methods such as HPLC or affinity chromatography.

Monoclonal antibodies of the present invention also include anti-idiotypic antibodies produced by methods well-known in the art. Monoclonal antibodies according to the present invention also may be monoclonal heteroconjugates, (i.e., hybrids of two or more antibody molecules). In another embodiment, monoclonal antibodies according to the invention are chimeric monoclonal antibodies. In one approach, the chimeric monoclonal antibody is engineered by cloning recombinant DNA containing the promoter, leader, and variable-region sequences from a mouse anti-PSA producing cell and the constant-region exons from a human antibody gene. The antibody encoded by such a recombinant gene is a mouse-human chimera. Its antibody specificity is determined by the variable region derived from mouse sequences. Its isotype, which is determined by the constant region, is derived from human DNA.

In another embodiment, the monoclonal antibody according to the present invention is a "humanized" monoclonal antibody, produced by any one of a number of techniques well-known in the art. That is, mouse complementary determining regions ("CDRs") are transferred from heavy and light V-chains of the mouse Ig into a human V-domain, followed by the replacement of some human residues in the framework regions of their

murine counterparts. "Humanized" monoclonal antibodies in accordance with this invention are especially suitable for use *in vivo* in diagnostic and therapeutic methods.

As stated above, the monoclonal antibodies and fragments thereof according to this invention are multiplied according to *in vitro* and *in vivo* methods well-known in the art. Multiplication *in vitro* is carried out in suitable culture media such as Dulbecco's modified Eagle medium or RPMI 1640 medium, optionally replenished by a mammalian serum such as fetal calf serum or trace elements and growth-sustaining supplements, e.g., feeder cells, such as normal mouse peritoneal exudate cells, spleen cells, bone marrow macrophages or the like. In vitro production provides relatively pure antibody preparations and allows scale-up to give large amounts of the desired antibodies. Techniques for large scale hybridoma cultivation under tissue culture conditions are known in the art and include homogenous suspension culture, (e.g., in an airlift reactor or in a continuous stirrer reactor or immobilized or entrapped cell culture).

Large amounts of the monoclonal antibody of the present invention also may be obtained by multiplying hybridoma cells *in vivo*. Cell clones are injected into mammals which are histocompatible with the parent cells, (e.g., syngeneic mice, to cause growth of antibody-producing tumors. Optionally, the animals are primed with a hydrocarbon, especially oils such as Pristane (tetramethylpentadecane) prior to injection.

In accordance with the present invention, fragments of the monoclonal antibody of the invention are obtained from monoclonal antibodies produced as described above, by methods which include digestion with enzymes such as pepsin or papain and/or cleavage of disulfide bonds by chemical reduction. Alternatively, monoclonal antibody fragments encompassed by the present invention are synthesized using an automated peptide synthesizer, or they may be produced manually using techniques well known in the art.

The monoclonal conjugates of the present invention are prepared by methods known in the art, e.g., by reacting a monoclonal antibody prepared as described above with, for instance, an enzyme in the presence of a coupling agent such as glutaraldehyde or periodate. Conjugates with fluorescein markers are prepared in the presence of these coupling agents, or by reaction with an isothiocyanate. Conjugates with metal chelates are similarly produced. Other moieties to which antibodies may be conjugated include

radionuclides such as, for example; ^{3}H, ^{125}I, ^{32}P, ^{35}S, ^{14}C, ^{51}Cr, ^{36}Cl, ^{57}Co, ^{58}Co, ^{59}Fe, ^{75}Se, and ^{152}Eu.

Radioactively labeled monoclonal antibodies of the present invention are produced according to well-known methods in the art. For instance, monoclonal antibodies are iodinated by contact with sodium or potassium iodide and a chemical oxidizing agent such as sodium hypochlorite, or an enzymatic oxidizing agent, such as lactoperoxidase. Monoclonal antibodies according to the invention may be labeled with technetium^{99} by ligand exchange process, for example, by reducing pertechnetate with stannous solution, chelating the reduced technetium onto a Sephadex column and applying the antibody to this column or by direct labeling techniques, (e.g., by incubating pertechnate, a reducing agent such as $SNCl_2$, a buffer solution such as sodium-potassium phthalate solution, and the antibody).

Any immunoassay may be used to monitor antibody production by the diagnostic/prognostic protein or immunogenic fragment or epitope thereof . Immunoassays, in their most simple and direct sense, are binding assays. Certain preferred immunoassays are the various types of enzyme linked immunosorbent assays (ELISAs) and radioimmunoassays (RIA) known in the art. Immunohistochemical detection using tissue sections is also particularly useful. However, it will be readily appreciated that detection is not limited to such techniques, and Western blotting, dot blotting, FACS analyses, and the like may also be used.

Most preferably, the assay will be capable of generating quantitative results.

For example, antibodies are tested in simple competition assays. A known antibody preparation that binds to the B cell epitope and the test antibody are incubated with an antigen composition comprising the B cell epitope, preferably in the context of the native antigen. "Antigen composition" as used herein means any composition that contains some version of the B cell epitope in an accessible form. Antigen-coated wells of an ELISA plate are particularly preferred. In one embodiment, one would pre-mix the known antibodies with varying amounts of the test antibodies (e.g., 1:1, 1:10 and 1:100) for a period of time prior to applying to the antigen composition. If one of the known antibodies is labeled, direct detection of the label bound to the antigen is possible; comparison to an unmixed sample assay will determine competition by the test antibody and, hence, cross-

reactivity. Alternatively, using secondary antibodies specific for either the known or test antibody, one will be able to determine competition.

An antibody that binds to the antigen composition will be able to effectively compete for binding of the known antibody and thus will significantly reduce binding of the latter. The reactivity of the known antibodies in the absence of any test antibody is the control. A significant reduction in reactivity in the presence of a test antibody is indicative of a test antibody that binds to the B cell epitope (i.e., it cross-reacts with the known antibody).

In one exemplary ELISA, the antibodies against the diagnostic/prognostic protein or immunogenic fragment or B cell epitope are immobilized onto a selected surface exhibiting protein affinity, such as a well in a polystyrene microtiter plate. Then, a composition containing a peptide comprising the B cell epitope is added to the wells. After binding and washing to remove non-specifically bound immune complexes, the bound epitope may be detected. Detection is generally achieved by the addition of a second antibody that is known to bind to the B cell epitope and is linked to a detectable label. This type of ELISA is a simple "sandwich ELISA". Detection may also be achieved by the addition of said second antibody, followed by the addition of a third antibody that has binding affinity for the second antibody, with the third antibody being linked to a detectable label.

Antibodies of the invention may be bound to a solid support and/or packaged into kits in a suitable container along with suitable reagents, controls, instructions and the like.

Immunoassay formats

In one embodiment, a cancer-associated protein or an immunogenic fragment or epitope thereof is detected in a patient sample, wherein the level of the protein or immunogenic fragment or epitope in the sample is indicative of ovarian cancer or disease recurrence or an indicator of poor survival. Preferably, the method comprises contacting a biological sample derived from the subject with an antibody capable of binding to a cancer-associated protein or an immunogenic fragment or epitope thereof, and detecting the formation of an antigen-antibody complex.

In another embodiment, an antibody against a cancer-associated protein or epitope thereof is detected in a patient sample, wherein the level of the antibody in the sample is indicative of ovarian cancer or disease recurrence or an indicator of poor survival.

Preferably, the method comprises contacting a biological sample derived from the subject with a cancer-associated protein or an antigenic fragment eg., a B cell epitope or other immunogenic fragment thereof, and detecting the formation of an antigen-antibody complex.

The diagnostic assays of the invention are useful for determining the progression of ovarian cancer or a metastasis thereof in a subject. In accordance with these prognostic applications of the invention, the level of a cancer-associated protein or an immunogenic fragment or epitope thereof in a biological sample is correlated with the disease state eg., as determined by clinical symptoms or biochemical tests (eg., CA125 levels).

Accordingly, a further embodiment of the invention provides a method for detecting a cancer cell in a subject, said method comprising:

(i) determining the level of a cancer-associate protein in a test sample from said subject; and

(ii) comparing the level determined at (i) to the level of said cancer-associated protein in a comparable sample from a healthy or normal individual,

wherein a level of said cancer-associate protein at (i) that is modified in the test sample relative to the comparable sample from the normal or healthy individual is indicative of the presence of a cancer cell in said subject.

In one embodiment of the diagnostic/prognostic methods described herein, the biological sample is obtained previously from the subject. In accordance with such an embodiment, the prognostic or diagnostic method is performed *ex vivo*.

In yet another embodiment, the subject diagnostic/prognostic methods further comprise processing the sample from the subject to produce a derivative or extract that comprises the analyte.

Preferred detection systems contemplated herein include any known assay for detecting proteins or antibodies in a biological sample isolated from a human subject, such as, for example, SDS/PAGE, isoelectric focussing, 2-dimensional gel electrophoresis comprising SDS/PAGE and isoelectric focussing, an immunoassay, a detection based system using an antibody or non-antibody ligand of the protein, such as, for example, a small molecule (e.g. a chemical compound, agonist, antagonist, allosteric modulator, competitive inhibitor, or non-competitive inhibitor, of the protein). In accordance with

these embodiments, the antibody or small molecule may be used in any standard solid phase or solution phase assay format amenable to the detection of proteins. Optical or fluorescent detection, such as, for example, using mass spectrometry, MALDI-TOF, biosensor technology, evanescent fiber optics, or fluorescence resonance energy transfer, is clearly encompassed by the present invention. Assay systems suitable for use in high throughput screening of mass samples, particularly a high throughput spectroscopy resonance method (e.g. MALDI-TOF, electrospray MS or nano-electrospray MS), are particularly contemplated.

Immunoassay formats are particularly preferred, eg., selected from the group consisting of, an immunoblot, a Western blot, a dot blot, an enzyme linked immunosorbent assay (ELISA), radioimmunoassay (RIA), enzyme immunoassay. Modified immunoassays utilizing fluorescence resonance energy transfer (FRET), isotope-coded affinity tags (ICAT), matrix-assisted laser desorption/ionization time of flight (MALDI-TOF), electrospray ionization (ESI), biosensor technology, evanescent fiber-optics technology or protein chip technology are also useful.

Preferably, the assay is a semi-quantitative assay or quantitative assay.

Standard solid phase ELISA formats are particularly useful in determining the concentration of a protein or antibody from a variety of patient samples.

In one form such as an assay involves immobilising a biological sample comprising antibodies against the cancer-associated protein or epitope, or alternatively an ovarian cancer-associated protein or an immunogenic fragment thereof, onto a solid matrix, such as, for example a polystyrene or polycarbonate microwell or dipstick, a membrane, or a glass support (e.g. a glass slide).

In the case of an antigen-based assay, an antibody that specifically binds an ovarian cancer-associated protein is brought into direct contact with the immobilised biological sample, and forms a direct bond with any of its target protein present in said sample. For an antibody-based assay, an immobilized ovarian cancer-associated protein or an immunogenic fragment or epitope thereof is contacted with the sample. The added antibody or protein in solution is generally labelled with a detectable reporter molecule, such as for example, a fluorescent label (e.g. FITC or Texas Red) or an enzyme (e.g. horseradish peroxidase (HRP)), alkaline phosphatase (AP) or β-galactosidase.

Alternatively, or in addition, a second labelled antibody can be used that binds to the first antibody or to the isolated/recombinant antigen. Following washing to remove any unbound antibody or antigen, as appropriate, the label is detected either directly, in the case of a fluorescent label, or through the addition of a substrate, such as for example hydrogen peroxide, TMB, or toluidine, or 5-bromo-4-chloro-3-indol-beta-D-galaotopyranoside (x-gal).

Such ELISA based systems are particularly suitable for quantification of the amount of a protein or antibody in a sample, such as, for example, by calibrating the detection system against known amounts of a standard.

In another form, an ELISA consists of immobilizing an antibody that specifically binds an ovarian cancer-associated protein on a solid matrix, such as, for example, a membrane, a polystyrene or polycarbonate microwell, a polystyrene or polycarbonate dipstick or a glass support. A patient sample is then brought into physical relation with said antibody, and the antigen in the sample is bound or 'captured'. The bound protein can then be detected using a labelled antibody. For example if the protein is captured from a human sample, an anti-human antibody is used to detect the captured protein. Alternatively, a third labelled antibody can be used that binds the second (detecting) antibody.

It will be apparent to the skilled person that the assay formats described herein are amenable to high throughput formats, such as, for example automation of screening processes, or a microarray format as described in Mendoza *et al*, Biotechniques 27(4): 778-788, 1999. Furthermore, variations of the above described assay will be apparent to those skilled in the art, such as, for example, a competitive ELISA.

Alternatively, the presence of antibodies against the cancer-associate protein, or alternatively an oarian cancer-associated protein or an immunogenic fragment thereof, is detected using a radioimmunoassay (RIA). The basic principle of the assay is the use of a radiolabelled antibody or antigen to detect antibody antigen interactions. For example, an antibody that specifically binds to an ovarian cancer-associated protein can be bound to a solid support and a biological sample brought into direct contact with said antibody. To detect the bound antigen, an isolated and/or recombinant form of the antigen is radiolabelled is brought into contact with the same antibody. Following washing the amount of bound radioactivity is detected. As any antigen in the biological sample inhibits binding of the radiolabelled antigen the amount of radioactivity detected is inversely

proportional to the amount of antigen in the sample. Such an assay may be quantitated by using a standard curve using increasing known concentrations of the isolated antigen.

As will be apparent to the skilled artisan, such an assay may be modified to use any reporter molecule, such as, for example, an enzyme or a fluorescent molecule, in place of a radioactive label.

Western blotting is also useful for detecting an ovarian cancer-associated protein or an immunogenic fragment thereof. In such an assay protein from a biological sample is separated using sodium dodecyl sulphate (SDS) polyacrylamide gel electrophoresis (SDS-PAGE) using techniques well known in the art and described in, for example, Scopes (*In:* Protein Purification: Principles and Practice, Third Edition, Springer Verlag, 1994). Separated proteins are then transferred to a solid support, such as, for example, a membrane or more specifically PVDF membrane, using methods well known in the art, for example, electrotransfer. This membrane may then be blocked and probed with a labelled antibody or ligand that specifically binds an ovarian cancer-associated protein. Alternatively, a labelled secondary, or even tertiary, antibody or ligand can be used to detect the binding of a specific primary antibody.

High-throughput methods for detecting the presence or absence of antibodies, or alternatively ovarian cancer-associated protein or an immunogenic fragment thereof are particularly preferred.

In one embodiment, MALDI-TOF is used for the rapid identification of a protein. Accordingly, there is no need to detect the proteins of interest using an antibody or ligand that specifically binds to the protein of interest. Rather, proteins from a biological sample are separated using gel electrophoresis using methods well known in the art and those proteins at approximately the correct molecular weight and/or isoelectric point are analysed using MALDI-TOF to determine the presence or absence of a protein of interest.

Alternatively, MALDI or ESI or a combination of approaches is used to determine the concentration of a particular protein in a biological sample, such as, for example sputum. Such proteins are preferably well characterised previously with regard to parameters such as molecular weight and isoelectric point.

Biosensor devices generally employ an electrode surface in combination with current or impedance measuring elements to be integrated into a device in combination with the assay substrate (such as that described in U.S. Patent No. 5,567,301). An antibody or ligand that specifically binds to a protein of interest Is preferably incorporated onto the surface of a biosensor device and a biological sample isolated from a patient (for example sputum that has been solubilised using the methods described herein) contacted to said device. A change in the detected current or impedance by the biosensor device indicates protein binding to said antibody or ligand. Some forms of biosensors known in the art also rely on surface plasmon resonance to detect protein interactions, whereby a change in the surface plasmon resonance surface of reflection is indicative of a protein binding to a ligand or antibody (U.S. Patent No. 5,485,277 and 5,492,840).

Biosensors are of particular use in high throughput analysis due to the ease of adapting such systems to micro- or nano-scales. Furthermore, such systems are conveniently adapted to incorporate several detection reagents, allowing for multiplexing of diagnostic reagents in a single biosensor unit. This permits the simultaneous detection of several epitopes in a small amount of body fluids.

Evanescent biosensors are also preferred as they do not require the pretreatment of a biological sample prior to detection of a protein of interest. An evanescent biosensor generally relies upon light of a predetermined wavelength interacting with a fluorescent molecule, such as for example, a fluorescent antibody attached near the probe's surface, to emit fluorescence at a different wavelength upon binding of the diagnostic protein to the antibody or ligand.

To produce protein chips, the proteins, peptides, polypeptides, antibodies or ligands that are able to bind specific antibodies or proteins of interest are bound to a solid support such as for example glass, polycarbonate, polytetrafluoroethylene, polystyrene, silicon oxide, metal or silicon nitride. This immobilization is either direct (e.g. by covalent linkage, such as, for example, Schiff's base formation, disulfide linkage, or amide or urea bond formation) or indirect. Methods of generating a protein chip are known in the art and are described in for example U.S. Patent Application No. 20020136821, 20020192654, 20020102617 and U.S. Patent No. 6,391,625. In order to bind a protein to a solid support it is often necessary to treat the solid support so as to create chemically reactive groups on the surface, such as, for example, with an aldehyde-containing silane reagent.

Alternatively, an antibody or ligand may be captured on a microfabricated polyacrylamide gel pad and accelerated into the gel using microelectrophoresis as described in, Arenkov *et al. Anal. Biochem. 278*:123-131, 2000.

A protein chip is preferably generated such that several proteins, ligands or antibodies are arrayed on said chip. This format permits the simultaneous screening for the presence of several proteins in a sample.

Alternatively, a protein chip may comprise only one protein, ligand or antibody, and be used to screen one or more patient samples for the presence of one polypeptide of interest. Such a chip may also be used to simultaneously screen an array of patient samples for a polypeptide of interest.

Preferably, a sample to be analysed using a protein chip is attached to a reporter molecule, such as, for example, a fluorescent molecule, a radioactive molecule, an enzyme, or an antibody that is detectable using methods well known in the art. Accordingly, by contacting a protein chip with a labelled sample and subsequent washing to remove any unbound proteins the presence of a bound protein is detected using methods well known in the art, such as, for example using a DNA microarray reader.

Alternatively, biomolecular interaction analysis-mass spectrometry (BIA-MS) is used to rapidly detect and characterise a protein present in complex biological samples at the low- to sub-fmole level (Nelson *et al. Electrophoresis 21*: 1155-1163, 2000). One technique useful in the analysis of a protein chip is surface enhanced laser desorption/ionization-time of flight-mass spectrometry (SELDI-TOF-MS) technology to characterise a protein bound to the protein chip. Alternatively, the protein chip is analysed using ESI as described in U.S. Patent Application 20020139751.

As will be apparent to the skilled artisan, protein chips are particularly amenable to multiplexing of detection reagents. Accordingly, several antibodies or ligands each able to specifically bind a different peptide or protein may be bound to different regions of said protein chip. Analysis of a biological sample using said chip then permits the detecting of multiple proteins of interest, or multiple B cell epitopes of the ovarian cancer-associated protein. Multiplexing of diagnostic and prognostic markers is particularly contemplated in the present invention.

In a further embodiment, the samples are analysed using ICAT, essentially as described in US Patent Application No. 20020076739. This system relies upon the labelling of a protein sample from one source (i.e. a healthy individual) with a reagent and the labelling of a protein sample from another source (i.e. a tuberculosis patient) with a second reagent that is chemically identical to the first reagent, but differs in mass due to isotope composition. It is preferable that the first and second reagents also comprise a biotin molecule. Equal concentrations of the two samples are then mixed, and peptides recovered by avidin affinity chromatography. Samples are then analysed using mass spectrometry. Any difference in peak heights between the heavy and light peptide ions directly correlates with a difference in protein abundance in a biological sample. The identity of such proteins may then be determined using a method well known in the art, such as, for example MALDI-TOF, or ESI.

As will be apparent to those skilled in the art a diagnostic or prognostic assay described herein may be a multiplexed assay. As used herein the term "multiplex", shall be understood not only to mean the detection of two or more diagnostic or prognostic markers in a single sample simultaneously, but also to encompass consecutive detection of two or more diagnostic or prognostic markers in a single sample, simultaneous detection of two or more diagnostic or prognostic markers in distinct but matched samples, and consecutive detection of two or more diagnostic or prognostic markers in distinct but matched samples. As used herein the term "matched samples" shall be understood to mean two or more samples derived from the same initial biological sample, or two or more biological samples isolated at the same point in time.

Accordingly, a multiplexed assay may comprise an assay that detects several antibodies and/or epitopes in the same reaction and simultaneously, or alternatively, it may detect other one or more antigens/antibodies in addition to one or more antibodies and/or epitopes. As will be apparent to the skilled artisan, if such an assay is antibody or ligand based, both of these antibodies must function under the same conditions.

Diagnostic assay kits

A further aspect of the present invention provides a kit for detecting *M. tuberculosis* infection in a biological sample. In one embodiment, the kit comprises:

(i) one or more isolated antibodies that bind to an ovarian cancer-associated protein or an immunogenic fragment or epitope thereof; and

(ii) means for detecting the formation of an antigen-antibody complex.

In an alternative embodiment, the kit comprises:

(i) an isolated or recombinant ovarian cancer-associated protein or an immunogenic fragment or epitope thereof; and

(ii) means for detecting the formation of an antigen-antibody complex.

Optionally, the kit further comprises means for the detection of the binding of an antibody, fragment thereof or a ligand to an ovarian cancer-associated protein. Such means include a reporter molecule such as, for example, an enzyme (such as horseradish peroxidase or alkaline phosphatase), a substrate, a cofactor, an inhibitor, a dye, a radionucleotide, a luminescent group, a fluorescent group, biotin or a colloidal particle, such as colloidal gold or selenium. Preferably such a reporter molecule is directly linked to the antibody or ligand.

In yet another embodiment, a kit may additionally comprise a reference sample. Such a reference sample.

In another embodiment, a reference sample comprises a peptide that is detected by an antibody or a ligand. Preferably, the peptide is of known concentration. Such a peptide is of particular use as a standard. Accordingly various known concentrations of such a peptide may be detected using a prognostic or diagnostic assay described herein.

In yet another embodiment, a kit comprises means for protein isolation (Scopes (*In:* Protein Purification: Principles and Practice, Third Edition, Springer Verlag, 1994).

Bioinformatics

The ability to identify genes that are over or under expressed in ovarian cancer can additionally provide high-resolution, high-sensitivity datasets which are used in the areas of diagnostics, therapeutics, drug development, pharmacogenetics, protein structure, biosensor development, and other related areas. For example, the expression profiles are used in diagnostic or prognostic evaluation of patients with ovarian cancer. Or as another example, subcellular toxicological information are generated to better direct drug structure and activity correlation (*see* Anderson, *Pharmaceutical Proteomics: Targets, Mechanism, and Function,* paper presented at the IBC Proteomics conference, Coronado, CA (June 11-12, 1998)). Subcellular toxicological information can also be utilized in a biological sensor device to predict the likely toxicological effect of chemical

exposures and likely tolerable exposure thresholds *(see* U.S. Patent No. 5,811,231). Similar advantages accrue from datasets relevant to other biomolecules and bioactive agents (e.g., nucleic acids, saccharides, lipids, drugs, and the like).

Thus, in another embodiment, the present invention provides a database that includes at least one set of assay data. The data contained in the database is acquired, e.g., using array analysis either singly or in a library format. The database are in substantially any form in which data are maintained and transmitted, but is preferably an electronic database. The electronic database of the invention are maintained on any electronic device allowing for the storage of and access to the database, such as a personal computer, but is preferably distributed on a wide area network, such as the World Wide Web.

The focus of the present section on databases that include peptide sequence data is for clarity of illustration only. It will be apparent to those of skill in the art that similar databases are assembled for any assay data acquired using an assay of the invention.

The compositions and methods for identifying and/or quantitating the relative and/or absolute abundance of a variety of molecular and macromolecular species from a biological sample undergoing ovarian cancer, i.e., the identification of ovarian cancer-associated sequences described herein, provide an abundance of information, which are correlated with pathological conditions, predisposition to disease, drug testing, therapeutic monitoring, gene-disease causal linkages, identification of correlates of immunity and physiological status, among others. Although the data generated from the assays of the invention is suited for manual review and analysis, in a preferred embodiment, prior data processing using high-speed computers is utilized.

An array of methods for indexing and retrieving biomolecular information is known in the art. For example, U.S. Patents 6,023,659 and 5,966,712 disclose a relational database system for storing biomolecular sequence information in a manner that allows sequences to be catalogued and searched according to one or more protein function hierarchies. U.S. Patent 5,953,727 discloses a relational database having sequence records containing information in a format that allows a collection of partial-length DNA sequences to be catalogued and searched according to association with one or more sequencing projects for obtaining full-length sequences from the collection of partial length sequences. U.S. Patent 5,706,498 discloses a gene database retrieval system for

making a retrieval of a gene sequence similar to a sequence data item in a gene database based on the degree of similarity between a key sequence and a target sequence. U.S. Patent 5,538,897 discloses a method using mass spectroscopy fragmentation patterns of peptides to identify amino acid sequences in computer databases by comparison of predicted mass spectra with experimentally-derived mass spectra using a closeness-of-fit measure. U.S. Patent 5,926,818 discloses a multi-dimensional database comprising a functionality for multi-dimensional data analysis described as on-line analytical processing (OLAP), which entails the consolidation of projected and actual data according to more than one consolidation path or dimension. U.S. Patent 5,295,261 reports a hybrid database structure in which the fields of each database record are divided into two classes, navigational and informational data, with navigational fields stored in a hierarchical topological map which are viewed as a tree structure or as the merger of two or more such tree structures.

See also Mount *et al., Bioinformatics (2001); Biological Sequence Analysis: Probabilistic Models of Proteins and Nucleic Acids* (Durbin *et al.*, eds., 1999); *Bioiraformatics: A Practical Guide to the Analysis of Genes and Proteins* (Baxevanis & Oeullette eds., 1998)); Rashidi & Buehler, *Bioinformatics: Basic Applications in Biological Science and Medicine* (1999); *Introduction to Computational Molecular Biology* (Setubal *et al.*, eds 1997); *Bioinformatics: Methods and Protocols* (Misener & Krawetz, eds, *2000); Bioinformatics: Sequence, Structure, and Databanks: A Practical Approach* (Higgins & Taylor, eds., 2000); Brown, *Bioinfor7natics: A Biologist's Guide to Biocomputing and the Internet (2001);* Han & Kamber, *Data Mining: Concepts and Techniques (2000);* and Waterman, *Introduction to Computational Biology: Maps, Sequences, and Genomes* (1995).

The present invention provides a computer database comprising a computer and software for storing in computer-retrievable form assay data records cross-tabulated, e.g., with data specifying the source of the target-containing sample from which each sequence specificity record was obtained.

In an exemplary embodiment, at least one of the sources of target-containing sample is from a control tissue sample known to be free of pathological disorders. In a variation, at least one of the sources is a known pathological tissue specimen, e.g., a neoplastic lesion or another tissue specimen to be analyzed for prostate cancer. In another variation, the assay records cross-tabulate one or more of the following parameters for

each target species in a sample: (1) a unique identification code, which can include, e.g., a target molecular structure and/or characteristic separation coordinate (e.g., electrophoretic coordinates); (2) sample source; and (3) absolute and/or relative quantity of the target species present in the sample.

The invention also provides for the storage and retrieval of a collection of target data in a computer data storage apparatus, which can include magnetic disks, optical disks, magneto-optical disks, DRAM, SRAM, SGRAM, SDRAM, RDRAM, DDR RAM, magnetic bubble memory devices, and other data storage devices, including CPU registers and on-CPU data storage arrays. Typically, the target data records are stored as a bit pattern in an array of magnetic domains on a magnetizable medium or as an array of charge states or transistor gate states, such as an array of cells in a DRAM device (e.g., each cell comprised of a transistor and a charge storage area, which are on the transistor). In one embodiment, the invention provides such storage devices, and computer systems built therewith, comprising a bit pattern encoding a protein expression fingerprint record comprising unique identifiers for at least 10 target data records cross-tabulated with target source.

When the target is a peptide or nucleic acid, the invention preferably provides a method for identifying related peptide or nucleic acid sequences, comprising performing a computerised comparison between a peptide or nucleic acid sequence assay record stored in or retrieved from a computer storage device or database and at least one other sequence. The comparison can include a sequence analysis or comparison algorithm or computer program embodiment thereof (e.g., BLAST, FASTA, TFASTA, GAP, BESTFIT – see above) and/or the comparison are of the relative amount of a peptide or nucleic acid sequence in a pool of sequences determined from a polypeptide or nucleic acid sample of a specimen.

The invention also preferably provides a magnetic disk, such as an IBM-compatible (DOS, Windows, Windows95/.98/2000, Windows NT, OS/2) or other format (e.g., Linux, SunOS, Solaris, AIX, SCO Unix, VMS, MV; Macintosh, etc.) floppy diskette or hard (fixed, Winchester) disk drive, comprising a bit pattern encoding data from an assay of the invention in a file format suitable for retrieval and processing in a computerized sequence analysis, comparison, or relative quantitation method.

The invention also provides a network, comprising a plurality of computing devices linked via a data link, such as an Ethernet cable (coax or IOBaseT), telephone line, ISDN line, wireless network, optical fiber, or other suitable signal transmission medium, whereby at least one network device (e.g., computer, disk array, etc.) comprises a pattern of magnetic domains (e.g., magnetic disk) and/or charge domains (e.g., an array of DRAM cells) composing a bit pattern encoding data acquired from an assay of the invention.

The invention also provides a method for transmitting assay data that includes generating an electronic signal on an electronic communications device, such as a modem, ISDN terminal adapter, DSL, cable modem, ATM switch, or the like, wherein the signal includes (in native or encrypted format) a bit pattern encoding data from an assay or a database comprising a plurality of assay results obtained by the method of the invention.

In a preferred embodiment, the invention provides a computer system for comparing a query target to a database containing an array of data structures, such as an assay result obtained by the method of the invention, and ranking database targets based on the degree of identity and gap weight to the target data. A central processor is preferably initialized to load and execute the computer program for alignment and/or comparison of the assay results. Data for a query target is entered into the central processor via an I/O device. Execution of the computer program results in the central processor retrieving the assay data from the data file, which comprises a binary description of an assay result.

The target data or record and the computer program are transferred to secondary memory, which is typically random access memory (e.g., DRAM, SRAM, SGRAM, or SDRAM). Targets are ranked according to the degree of correspondence between a selected assay characteristic (e.g., binding to a selected affinity moiety) and the same characteristic of the query target and results are output via an I/O device. For example, a central processor are a conventional computer (e.g., Intel Pentium, PowerPC, Alpha, PA-8000, SPARC, MIPS 4400, MIPS 10000, VAX, etc.); a program are a commercial or public domain molecular biology software package (e.g., UWGCG Sequence Analysis Software, Darwin); a data file are an optical or magnetic disk, a data server, a memory device (e.g., DRAM, SRAM, SGRAM, SDRAM, EPROM, bubble memory, flash memory, etc.); an I/O device are a terminal comprising a video display and a keyboard, a modem, an ISDN terminal adapter, an Ethernet port, a punched card reader, a magnetic strip reader, or other suitable I/O device.

The invention also preferably provides the use of a computer system, such as that described above, which comprises: (1) a computer; (2) a stored bit pattern encoding a collection of peptide sequence specificity records obtained by the methods of the invention, which are stored in the computer; (3) a comparison target, such as a query target; and (4) a program for alignment and comparison, typically with rank-ordering of comparison results on the basis of computed similarity values.

Transgenic Animals Expressing Ovarian Cancer-associated proteins and "Knock-Out" Animals

The present invention also contemplates transgenic animals which are transgenic by virtue of comprising a polynucleotide of the invention, i.e. animals transformed with a cancer-associated gene of the invention. Suitable animals are generally from the phylum chordata. Chordates includes vertebrate groups such as mammals, birds, reptiles and amphibians. Particular examples of mammals include non-human primates, cats, dogs, ungulates such as cows, goats, pigs, sheep and horses and rodents such as mice, rats, gerbils and hamsters. Transgenic animals within the meaning of the present invention are non-human animals and the production of transgenic humans is specifically excluded.

Techniques for producing transgenic animals are well known in the art. A useful general textbook on this subject is Houdebine, Transgenic animals – Generation and Use (Harwood Academic, 1997) – an extensive review of the techniques used to generate transgenic animals from fish to mice and cows.

Advances in technologies for embryo micromanipulation now permit introduction of heterologous DNA into, for example, fertilized mammalian ova. For instance, totipotent or pluripotent stem cells are transformed by microinjection, calcium phosphate mediated precipitation, liposome fusion, retroviral infection or other means, the transformed cells are then introduced into the embryo, and the embryo then develops into a transgenic animal. In a highly preferred method, developing embryos are infected with a retrovirus containing the desired DNA, and transgenic animals produced from the infected embryo. In a most preferred method, however, the appropriate DNAs are coinjected into the pronucleus or cytoplasm of embryos, preferably at the single cell stage, and the embryos allowed to develop into mature transgenic animals. Those techniques as well known. See reviews of standard laboratory procedures for microinjection of heterologous DNAs into

mammalian fertilized ova, including Hogan *et al.*, Manipulating the Mouse Embryo, (Cold Spring Harbor Press 1986); Krimpenfort *et al.*, Bio/Technology 9:844 (1991); Palmiter *et al.*, Cell, 41: 343 (1985); Kraemer *et al.*, Genetic manipulation of the Mammalian Embryo, (Cold Spring Harbor Laboratory Press 1985); Hammer *et al.*, Nature, 315: 680 (1985); Wagner *et al.*, U.S. Pat. No. 5,175,385; Krimpenfort *et al.*, U.S. Pat. No. 5,175,384, the respective contents of which are incorporated herein by reference

Another method used to produce a transgenic animal involves microinjecting a nucleic acid into pro-nuclear stage eggs by standard methods. Injected eggs are then cultured before transfer into the oviducts of pseudopregnant recipients.

Transgenic animals may also be produced by nuclear transfer technology as described in Schnieke, A.E. *et al.*, 1997, Science, 278: 2130 and Cibelli, J.B. *et al.*, 1998, Science, 280: 1256. Using this method, fibroblasts from donor animals are stably transfected with a plasmid incorporating the coding sequences for a binding domain or binding partner of interest under the control of regulatory. Stable transfectants are then fused to enucleated oocytes, cultured and transferred into female recipients.

Analysis of animals which may contain transgenic sequences would typically be performed by either PCR or Southern blot analysis following standard methods.

By way of a specific example for the construction of transgenic mammals, such as cows, nucleotide constructs comprising a sequence encoding a binding domain fused to GFP are microinjected using, for example, the technique described in U.S. Pat. No. 4,873,191, into oocytes which are obtained from ovaries freshly removed from the mammal. The oocytes are aspirated from the follicles and allowed to settle before fertilization with thawed frozen sperm capacitated with heparin and prefractionated by Percoll gradient to isolate the motile fraction.

The fertilized oocytes are centrifuged, for example, for eight minutes at 15,000 g to visualize the pronuclei for injection and then cultured from the zygote to morula or blastocyst stage in oviduct tissue-conditioned medium. This medium is prepared by using luminal tissues scraped from oviducts and diluted in culture medium. The zygotes must be placed in the culture medium within two hours following microinjection.

Oestrous is then synchronized in the intended recipient mammals, such as cattle, by administering coprostanol. Oestrous is produced within two days and the embryos are transferred to the recipients 5-7 days after estrous. Successful transfer are evaluated in the offspring by Southern blot.

Alternatively, the desired constructs are introduced into embryonic stem cells (ES cells) and the cells cultured to ensure modification by the transgene. The modified cells are then injected into the blastula embryonic stage and the blastulas replaced into pseudopregnant hosts. The resulting offspring are chimeric with respect to the ES and host cells, and nonchimeric strains which exclusively comprise the ES progeny are obtained using conventional cross-breeding. This technique is described, for example, in WO91/10741.

In another embodiment, transgenic animals of the present invention are transgenic "knock-out" animals where a specific gene corresponding to a polynucleotide referred to in Tables 1-3 has been rendered non-functional by homologous recombination. The generation of "knock-out" animals is similar to the production of other transgenic animals except that the polynucleotide constructs are designed to integrate into the endogenous genes and disrupt the function of the endogenous sequences. The generation of "knock-out" animals is known in the art, including the design of suitable constructs that will recombine at the appropriate site in the genome.

In one embodiment, the heterologous sequence which it is desired to recombine into the genome of a target animal comprises a functional sequence but under the control of an inducible promoter so that expression of the gene are regulated by administration of an endogenous molecule. This are advantageous where disruption of the gene is embryonic-lethal.

"Knock-out" animals are used as animal models for the study of gene function.

Therapeutic peptides

In accordance with this embodiment, ovarian cancer-associated proteins of the present invention are administered therapeutically to patients for a time and under conditions sufficient to ameliorate the growth of a tumor in the subject or to prevent tumor recurrence.

It is preferred to use peptides that do not consisting solely of naturally-occurring amino acids but which have been modified, for example to reduce immunogenicity, to increase circulatory half-life in the body of the patient, to enhance bioavailability and/or to enhance efficacy and/or specificity.

A number of approaches have been used to modify peptides for therapeutic application. One approach is to link the peptides or proteins to a variety of polymers, such as polyethylene glycol (PEG) and polypropylene glycol (PPG) – see for example U.S. Patent Nos. 5,091,176, 5,214,131 and US 5,264,209.

Replacement of naturally-occurring amino acids with a variety of uncoded or modified amino acids such as D-amino acids and N-methyl amino acids may also be used to modify peptides

Another approach is to use bifunctional crosslinkers, such as N-succinimidyl 3-(2 pyridyldithio) propionate, succinimidyl 6-[3-(2 pyridyldithio) propionamido] hexanoate, and sulfosuccinimidyl 6-[3-(2 pyridyldithio) propionamido]hexanoate (see US Patent 5,580,853).

It are desirable to use derivatives of the ovarian cancer-associated proteins of the invention which are conformationally constrained. Conformational constraint refers to the stability and preferred conformation of the three-dimensional shape assumed by a peptide. Conformational constraints include local constraints, involving restricting the conformational mobility of a single residue in a peptide; regional constraints, involving restricting the conformational mobility of a group of residues, which residues may form some secondary structural unit; and global constraints, involving the entire peptide structure.

The active conformation of the peptide are stabilized by a covalent modification, such as cyclization or by incorporation of gamma-lactam or other types of bridges. For example, side chains are cyclized to the backbone so as create a L-gamma-lactam moiety on each side of the interaction site. See, generally, Hruby et al., "Applications of Synthetic Peptides," in Synthetic Peptides: A User's Guide: 259-345 (W. H. Freeman & Co. 1992). Cyclization also are achieved, for example, by formation of cystine bridges, coupling of amino and carboxy terminal groups of respective terminal amino acids, or coupling of the amino group of a Lys residue or a related homolog with a carboxy group of Asp, Glu or a

related homolog. Coupling of the .alpha-amino group of a polypeptide with the epsilon-amino group of a lysine residue, using iodoacetic anhydride, are also undertaken. See Wood and Wetzel, 1992, Int'l J. Peptide Protein Res. 39: 533-39.

Another approach described in US 5,891,418 is to include a metal-ion complexing backbone in the peptide structure. Typically, the preferred metal-peptide backbone is based on the requisite number of particular coordinating groups required by the coordination sphere of a given complexing metal ion. In general, most of the metal ions that may prove useful have a coordination number of four to six. The nature of the coordinating groups in the peptide chain includes nitrogen atoms with amine, amide, imidazole, or guanidino functionalities; sulfur atoms of thiols or disulfides; and oxygen atoms of hydroxy, phenolic, carbonyl, or carboxyl functionalities. In addition, the peptide chain or individual amino acids are chemically altered to include a coordinating group, such as for example oxime, hydrazino, sulfhydryl, phosphate, cyano, pyridino, piperidino, or morpholino. The peptide construct are either linear or cyclic, however a linear construct is typically preferred. One example of a small linear peptide is Gly-Gly-Gly-Gly which has four nitrogens (an N_4 complexation system) in the back bone that can complex to a metal ion with a coordination number of four.

A further technique for improving the properties of therapeutic peptides is to use non-peptide peptidomimetics. A wide variety of useful techniques are used to elucidating the precise structure of a peptide. These techniques include amino acid sequencing, x-ray crystallography, mass spectroscopy, nuclear magnetic resonance spectroscopy, computer-assisted molecular modeling, peptide mapping, and combinations thereof. Structural analysis of a peptide generally provides a large body of data which comprise the amino acid sequence of the peptide as well as the three-dimensional positioning of its atomic components. From this information, non-peptide peptidomimetics are designed that have the required chemical functionalities for therapeutic activity but are more stable, for example less susceptible to biological degradation. An example of this approach is provided in US 5,811,512.

Techniques for chemically synthesising therapeutic peptides of the invention are described in the above references and also reviewed by Borgia and Fields, 2000, TibTech 18: 243-251 and described in detail in the references contained therein.

Assays for therapeutic compounds

The ovarian cancer proteins, nucleic acids, and antibodies as described herein are used in drug screening assays to identify candidate compounds for use in treating ovarian cancer. The ovarian cancer-associated proteins, antibodies, nucleic acids, modified proteins and cells containing ovarian cancer sequences are used in drug screening assays or by evaluating the effect of drug candidates on a "gene expression profile" or expression profile of polypeptides. In a preferred embodiment, the expression profiles are used, preferably in conjunction with high throughput screening techniques to allow monitoring for expression profile genes after treatment with a candidate agent (e.g., Zlokarnik, *et al.,* 1998, *Science* 279: 84-88); Heid, 1996, *Genome Res* 6: 986-94).

In a preferred embodiment, the ovarian cancer-associated proteins, antibodies, nucleic acids, modified proteins and cells containing the native or modified ovarian cancer-associated proteins are used in screening assays. That is, the present invention provides methods for screening for compounds/agents which modulate the ovarian cancer phenotype or an identified physiological function of a ovarian cancer-associated protein. As above, this are done on an individual gene level or by evaluating the effect of drug candidates on a "gene expression profile". In a preferred embodiment, the expression profiles are used, preferably in conjunction with high throughput screening techniques to allow monitoring for expression profile genes after treatment with a candidate agent, see Zlokarnik, supra.

Having identified the differentially expressed genes herein, a variety of assays are executed. In a preferred embodiment, assays are run on an individual gene or protein level. That is, having identified a particular gene as up regulated in ovarian cancer, test compounds are screened for the ability to modulate gene expression or for binding to the ovarian cancer-associated protein. "Modulation" thus includes both an increase and a decrease in gene expression. The preferred amount of modulation will depend on the original change of the gene expression in normal versus tissue undergoing ovarian cancer, with changes of at least 10%, preferably 50%, more preferably 100-300%, and in some embodiments 300-1000% or greater. Thus, if a gene exhibits a 4-fold increase in ovarian cancer tissue compared to normal tissue, a decrease of about four-fold is often desired; similarly, a 10-fold decrease in ovarian cancer tissue compared to normal tissue often provides a target value of a 10-fold increase in expression to be induced by the test compound.

The amount of gene expression are monitored using nucleic acid probes and the quantification of gene expression levels, or, alternatively, the gene product itself are monitored, e.g., through the use of antibodies to the ovarian cancer-associated protein and standard immunoassays. Proteomics and separation techniques may also allow quantification of expression. .

In a preferred embodiment, gene expression or protein monitoring of a number of entities, i.e., an expression profile, is monitored simultaneously. Such profiles will typically involve a plurality of those entities described herein.

In this embodiment, the ovarian cancer nucleic acid probes are attached to biochips as outlined herein for the detection and quantification of ovarian cancer sequences in a particular cell. Alternatively, PCR are used. Thus, a series are used with dispensed primers in desired wells. A PCR reaction can then be performed and analyzed for each well.

Expression monitoring are performed to identify compounds that modify the expression of one or more ovarian cancer-associated sequences, e.g., a polynucleotide sequence set out in Tables 1-3. In a preferred embodiment, a test modulator is added to the cells prior to analysis. Moreover, screens are also provided to identify agents that modulate ovarian cancer, modulate ovarian cancer-associated proteins, bind to a ovarian cancer-associated protein, or interfere with the binding of a ovarian cancer-associated protein and an antibody or other binding partner.

The term "test compound" or "drug candidate" or "modulator" or grammatical equivalents as used herein describes any molecule, e.g., protein, oligopeptide, small organic molecule, polysaccharide, polynucleotide, etc., to be tested for the capacity to directly or indirectly alter the ovarian cancer phenotype or the expression of a ovarian cancer sequence, e.g., a nucleic acid or protein sequence. In preferred embodiments, modulators alter expression profiles, or expression profile nucleic acids or proteins provided herein. In one embodiment, the modulator suppresses a ovarian cancer phenotype, e.g. to a normal tissue fingerprint. In another embodiment, a modulator induced a ovarian cancer phenotype. Generally, a plurality of assay mixtures are run in parallel with different agent concentrations to obtain a differential response to the various concentrations. Typically, one of these concentrations serves as a negative control, i.e., at zero concentration or below the level of detection.

Drug candidates encompass numerous chemical classes, though typically they are organic molecules, preferably small organic compounds having a molecular weight of more than 100 and less than about 2,500 daltons. Preferred small molecules are less than 2000, or less than 1500 or less than 1000 or less than 500 Daltons. Candidate agents comprise functional groups necessary for structural interaction with proteins, particularly hydrogen bonding, and typically include at least an amine, carbonyl, hydroxyl or carboxyl group, preferably at least two of the functional chemical groups. The candidate agents often comprise cyclical carbon or heterocyclic structures and/or aromatic or polyaromatic structures substituted with one or more of the above functional groups. Candidate agents are also found among biomolecules including peptides, saccharides, fatty acids, steroids, purines, pyrimidines, derivatives, structural analogs or combinations thereof. Particularly preferred are peptides.

In one aspect, a modulator will neutralize the effect of a ovarian cancer-associated protein. By "neutralize" is meant that activity of a protein is inhibited or blocked and the consequent effect on the cell.

In certain embodiments, combinatorial libraries of potential modulators will be screened for an ability to bind to a ovarian cancer polypeptide or to modulate activity. Conventionally, new chemical entities with useful properties are generated by identifying a chemical compound (called a "lead compound") with some desirable property or activity, e.g., inhibiting activity, creating variants of the lead compound, and evaluating the property and activity of those variant compounds. Often, high throughput screening (HTS) methods are employed for such an analysis.

In one preferred embodiment, high throughput screening methods involve providing a library containing a large number of potential therapeutic compounds (candidate compounds). Such "combinatorial chemical libraries" are then screened in one or more assays to identify those library members (particular chemical species or subclasses) that display a desired characteristic activity. The compounds thus identified can serve as conventional "lead compounds" or can themselves be used as potential or actual therapeutics.

A combinatorial chemical library is a collection of diverse chemical compounds generated by either chemical synthesis or biological synthesis by combining a number of chemical

"building blocks" such as reagents. For example, a linear combinatorial chemical library, such as a polypeptide (e.g., mutein) library, is formed by combining a set of chemical building blocks called amino acids in every possible way for a given compound length (i.e., the number of amino acids in a polypeptide compound). Millions of chemical compounds are synthesized through such combinatorial mixing of chemical building blocks (Gallop *et al.*, 1994, *J. Med. Chem.* 37(9):1233-1251).

Preparation and screening of combinatorial chemical libraries is well known to those of skill in the art. Such combinatorial chemical libraries include, but are not limited to, peptide libraries, peptoids, encoded peptides, random bio-oligomers, nonpeptidal peptidomimetics, analogous organic syntheses of small compound libraries, nucleic acid libraries, peptide nucleic acid libraries, antibody libraries, carbohydrate libraries and small organic molecule libraries.

The assays to identify modulators are amenable to high throughput screening. Preferred assays thus detect enhancement or inhibition of ovarian cancer gene transcription, inhibition or enhancement of polypeptide expression, and inhibition or enhancement of polypeptide activity.

High throughput assays for the presence, absence, quantification, or other properties of particular nucleic acids or protein products are well known to those of skill in the art. Similarly, binding assays and reporter gene assays are similarly well known. Thus, e.g., U.S. Patent No. 5,559,410 discloses high throughput screening methods for proteins, U.S. Patent No. 5,585,639 discloses high throughput screening methods for nucleic acid binding (i.e., in arrays), while U.S. Patent Nos. 5,576,220 and 5,541,061 disclose high throughput methods of screening for ligand/antibody binding.

In addition, high throughput screening systems are commercially available *(see, e.g.,* Zymark Corp., Hopkinton, MA; Air Technical Industries, Mentor, OH; Beckman Instruments, Inc. Fullerton, CA; Precision Systems, Inc., Natick, MA, *etc.).* These systems typically automate entire procedures, including all samlsle and reagent pipetting, liquid dispensing, timed incubations, and final readings of the microplate in detectors) appropriate for the assay. These configurable systems provide high throughput and rapid start up as well as a high degree of flexibility and customization. The manufacturers of such systems provide detailed protocols for various high throughput systems. Thus, e.g.,

Zymark Corp. provides technical bulletins describing screening systems for detecting the modulation of gene transcription, ligand binding, and the like.

In one embodiment, modulators are proteins, often naturally occurring proteins or fragments of naturally occurring proteins. Thus, e.g., cellular extracts containing proteins, or random or directed digests of proteinaceous cellular extracts, are used. In this way libraries of proteins are made for screening in the methods of the invention. Particularly preferred in this embodiment are libraries of bacterial, fungal, viral, and mammalian proteins, with the latter being preferred, and human proteins being especially preferred. Particularly useful test compound will be directed to the class of proteins to which the target belongs, e.g., substrates for enzymes or ligands and receptors.

In a preferred embodiment, modulators are peptides of from about 5 to about 30 amino acids, with from about 5 to about 20 amino acids being preferred, and from about 7 to about 15 being particularly preferred. The peptides are digests of naturally occurring proteins as is outlined above, random peptides, or "biased" random peptides. By "randomized" or grammatical equivalents herein is meant that each nucleic acid and peptide consists of essentially random nucleotides and amino acids, respectively. Since generally these random peptides (or nucleic acids, discussed below) are chemically synthesized, they may incorporate any nucleotide or amino acid at any position. The synthetic process are designed to generate randomized proteins or nucleic acids, to allow the formation of all or most of the possible combinations over the length of the sequence, thus forming a library of randomized candidate bioactive proteinaceous agents.

In one embodiment, the library is fully randomized, with no sequence preferences or constants at any position. In a preferred embodiment, the library is biased. That is, some positions within the sequence are either held constant, or are selected from a limited number of possibilities. For example, in a preferred embodiment, the nucleotides or amino acid residues are randomized within a defined class, e.g., of hydrophobic amino acids, hydrophilic residues, sterically biased (either small or large) residues, towards the creation of nucleic acid binding domains, the creation of cysteines, for cross-linking, prolines for SH-3 domains, serines, threonines, tyrosines or histidines for phosphorylation sites, etc., or to purines, etc.

Modulators of ovarian cancer can also be nucleic acids, as defined below. As described above generally for proteins, nucleic acid modulating agents are naturally occurring nucleic acids, random nucleic acids, or "biased" random nucleic acids. For example, digests of procaryotic or eucaryotic genomes are used as is outlined above for proteins.

In certain embodiments, the activity of a ovarian cancer-associated protein is down-regulated, or entirely inhibited, by the use of antisense polynucleotide, *i.e.,* a nucleic acid complementary to, and which can preferably hybridize specifically to, a coding mRNA nucleic acid sequence, e.g., a ovarian cancer-associated protein mRNA, or a subsequence thereof. Binding of the antisense polynucleotide to the mRNA reduces the translation and/or stability of the mRNA.

In the context of this invention, antisense polynucleotides can comprise naturally-occurring nucleotides, or synthetic species formed from naturally-occurring subunits or their close homologs. Antisense polynucleotides may also have altered sugar moieties or inter-sugar linkages. Exemplary among these are the phosphorothioate and other sulfur containing species which are known for use in the art. Analogs are comprehended by this invention so long as they function effectively to hybridize with the ovarian cancer-associated protein mRNA. *See, e.g.,* Isis Pharmaceuticals, Carlsbad, CA; Sequitor, Inc., Natick, MA.

Such antisense polynucleotides can readily be synthesized using recombinant means, or are synthesized *in vitro.* Equipment for such synthesis is sold by several vendors, including Applied Biosystems. The preparation of other oligonucleotides such as phosphorothioates and alkylated derivatives is also well known to those of skill in the art.

Antisense molecules as used herein include antisense or sense oligonucleotides. Sense oligonucleotides can, e.g., be employed to block transcription by binding to the anti-sense strand. The antisense and sense oligonucleotide comprise a single-stranded nucleic acid sequence (either RNA or DNA) capable of binding to target mRNA (sense) or DNA (antisense) sequences for ovarian cancer molecules. Antisense or sense oligonucleotides, according to the present invention, comprise a fragment generally at least about 14 nucleotides, preferably from about 14 to 30 nucleotides. The ability to derive an antisense or a sense oligonucleotide, based upon a cDNA sequence encoding a given protein is described in, e.g., Stein & Cohen *(Cancer Res.* 48:2659 (1988 and van der Krol *et al. (BioTechniques* 6:958 (1988)).

In addition to antisense polynucleotides, ribozymes are used to target and inhibit transcription of ovarian cancer-associated nucleotide sequences. A ribozyme is an RNA molecule that catalytically cleaves other RNA molecules. Different kinds of ribozymes have been described, including group I ribozymes, hammerhead ribozymes, hairpin ribozymes, RNase P, and axhead ribozymes *(see, e.g.,* Castanotto *et al., Adv. in Pharmacology 25: 289-317 (1994)* for a general review of the properties of different 5 ribozymes).

Methods of preparing ribozymes are well known to those of skill in the art *(see, e.g., WO 94/26877;* Ojwang *et al., Proc. Natl. Acad. Sci. USA 90:6340-6344 (1993);* Yamada *et al., Human Gene Therapy 1:39-45 (1994);* Leavitt *et al., Proc. Natl. Acad. Sci. USA 92:699- 703 (1995);* Leavitt *et al., Human Gene Therapy 5:1151-120 (1994);* and Yamada *et al., Virology 205: 121-126 (1994)).*

Polynucleotide modulators of ovarian cancer are introduced into a cell containing the target nucleotide sequence by formation of a conjugate with a ligand binding molecule, as described in WO 91/04753. Suitable ligand binding molecules include, but are not limited to, cell surface receptors, growth factors, other cytokines, or other ligands that bind to cell surface receptors. Preferably, conjugation of the ligand binding molecule does not substantially interfere with the ability of the ligand binding molecule to bind to its corresponding molecule or receptor, or block entry of the sense or antisense oligonucleotide or its conjugated version into the cell. Alternatively, a polynucleotide modulator of ovarian cancer are introduced into a cell containing the target nucleic acid sequence, e.g., by formation of an polynucleotide-lipid complex, as described in WO 90/10448. It is understood that the use of antisense molecules or knock out and knock in models may also be used in screening assays as discussed above, in addition to methods of treatment.

As noted above, gene expression monitoring is conveniently used to test candidate modulators (e.g., protein, nucleic acid or small molecule). After the candidate agent has been added and the cells allowed to incubate for some period of time, the sample containing a target sequence to be analyzed is added to the biochip. If required, the target sequence is prepared using known techniques. For example, the sample are treated to lyse the cells, using known lysis buffers, electroporation, etc., with purification and/or amplification such as PCR performed as appropriate. For example, an *in vitro*

transcription with labels covalently attached to the nucleotides is performed. Generally, the nucleic acids are labeled with biotin-FITC or PE, or with cy3 or cy5.

In a preferred embodiment, the target sequence is labeled with, e.g., a fluorescent, a chemiluminescent, a chemical, or a radioactive signal, to provide a means of detecting the target sequence's specific binding to a probe. The label also are an enzyme, such as, alkaline phosphatase or horseradish peroxidase, which when provided with an appropriate substrate produces a product that are detected. Alternatively, the label are a labeled compound or small molecule, such as an enzyme inhibitor, that binds but is not catalyzed or altered by the enzyme. The label also are a moiety or compound, such as, an epitope tag or biotin which specifically binds to streptavidin. For the example of biotin, the streptavidin is labeled as described above, thereby, providing a detectable signal for the bound target sequence. Unbound labeled streptavidin is typically removed prior to analysis.

As will be appreciated by those in the art, these assays are direct hybridization assays or can comprise "sandwich assays", which include the use of multiple probes, as is generally outlined in U.S. Patent Nos. 5,681,702, 5,597,909, 5,545,730, 5,594,117, 5,591,584, 5,571,670, 5,580,731, 5,571,670, 5,591,584, 5,624,802, 5,635,352, 5,594,118, 5,359,100, 5,124,246 and 5,681,697, all of which are hereby incorporated by reference. In this embodiment, in general, the target nucleic acid is prepared as outlined above, and then added to the biochip comprising a plurality of nucleic acid probes, under conditions that allow the formation of a hybridization complex.

A variety of hybridization conditions are used in the present invention, including high, moderate and low stringency conditions as outlined above. The assays are generally run under stringency conditions which allows formation of the label probe hybridization complex only in the presence of target. Stringency are controlled by altering a step parameter that is a thermodynamic variable, including, but not limited to, temperature, formamide concentration, salt concentration, chaotropic salt concentration pH, organic solvent concentration, etc.

These parameters may also be used to control non-specific binding, as is generally outlined in U.S. Patent No. 5,681,697. Thus it are desirable to perform certain steps at higher stringency conditions to reduce non-specific binding.

The reactions outlined herein are accomplished in a variety of ways. Components of the reaction are added simultaneously, or sequentially, in different orders, with preferred embodiments outlined below. In addition, the reaction may include a variety of other reagents. These include salts, buffers, neutral proteins, e.g. albumin, detergents, *etc.* which are used to facilitate optimal hybridization and detection, and/or reduce non-specific or background interactions. Reagents that otherwise improve the efficiency of the assay, such as protease inhibitors, nuclease inhibitors, anti-microbial agents, *etc.,* may also be used as appropriate, depending on the sample preparation methods and purity of the target.

The assay data are analyzed to determine the expression levels, and changes in expression levels as between states, of individual genes, forming a gene expression profile.

Screens are performed to identify modulators of the ovarian cancer phenotype. In one embodiment, screening is performed to identify modulators that can induce or suppress a particular expression profile, thus preferably generating the associated phenotype. In another embodiment, *e.g.,* for diagnostic applications, having identified differentially expressed genes important in a particular state, screens are performed to identify modulators that alter expression of individual genes. In an another embodiment, screening is performed to identify modulators that alter a biological function of the expression product of a differentially expressed gene. Again, having identified the importance of a gene in a particular state, screens are performed to identify agents that bind and/or modulate the biological activity of the gene product.

In addition screens are done for genes that are induced in response to a candidate agent. After identifying a modulator based upon its ability to suppress a ovarian cancer expression pattern leading to a normal expression pattern, or to modulate a single ovarian cancer gene expression profile so as to mimic the expression of the gene from normal tissue, a screen as described above are performed to identify genes that are specifically modulated in response to the agent. Comparing expression profiles between normal tissue and agent treated ovarian cancer tissue reveals genes that are not expressed in normal tissue or ovarian cancer tissue, but are expressed in agent treated tissue. These agent-specific sequences are identified and used by methods described herein for ovarian cancer genes or proteins. In particular these sequences and the proteins they encode find use in marking or identifying agent treated cells. In addition,

antibodies are raised against the agent induced proteins and used to target novel therapeutics to the treated ovarian cancer tissue sample.

Thus, in one embodiment, a test compound is administered to a population of ovarian cancer cells, that have an associated ovarian cancer expression profile. By "administration" or "contacting" herein is meant that the candidate agent is added to the cells in such a manner as to allow the agent to act upon the cell, whether by uptake and intracellular action, or by action at the cell surface. In some embodiments, nucleic acid encoding a proteinaceous candidate agent (i.e., a peptide) are put into a viral construct such as an adenoviral or retroviral construct, and added to the cell, such that expression of the peptide agent is accomplished. Regulatable gene administration systems can also be used.

Once the test compound has been administered to the cells, the cells are washed if desired and are allowed to incubate under preferably physiological conditions for some period of time. The cells are then harvested and a new gene expression profile is generated, as outlined herein.

Thus, e.g., ovarian cancer tissue are screened for agents that modulate, e.g., induce or suppress the ovarian cancer phenotype. A change in at least one gene, preferably many, of the expression profile indicates that the agent has an effect on ovarian cancer activity. By defining such a signature for the ovarian cancer phenotype, screens for new drugs that alter the phenotype are devised. With this approach, the drug target need not be known and need not be represented in the original expression screening platform, nor does the level of transcript for the target protein need to change.

In a preferred embodiment, as outlined above, screens are done on individual genes and gene products (proteins). That is, having identified a particular differentially expressed gene as important in a particular state, screening of modulators of either the expression of the gene or the gene product itself are done. The gene products of differentially expressed genes are sometimes referred to herein as "ovarian cancer-associated proteins" or a "ovarian cancer modulatory protein". The ovarian cancer modulatory protein are a fragment, or alternatively, be the full length protein to the fragment encoded by the nucleic acids referred to in Tables 1-3. Preferably, the ovarian cancer modulatory protein is a fragment. In a preferred embodiment, the ovarian cancer amino acid sequence which is used to determine sequence identity or similarity is encoded by a

nucleic acid referred to in Tables 1-3. In another embodiment, the sequences are naturally occurring allelic variants of a protein encoded by a nucleic acid referred to in Tables 1-3. In another embodiment, the sequences are sequence variants as further described herein.

Preferably, the ovarian cancer modulatory protein is a fragment of approximately 14 to 24 amino acids long. More preferably the fragment is a soluble fragment. Preferably, the fragment includes a non-transmembrane region. In a preferred embodiment, the fragment has an N-terminal Cys to aid in solubility. In one embodiment, the C-terminus of the fragment is kept as a free acid and the N-terminus is a free amine to aid in coupling, i.e., to cysteine.

In one embodiment the ovarian cancer-associated proteins are conjugated to an immunogenic agent as discussed herein. In one embodiment the ovarian cancer-associated protein is conjugated to BSA.

Measurements of ovarian cancer polypeptide activity, or of ovarian cancer or the ovarian cancer phenotype are performed using a variety of assays. For example, the effects of the test compounds upon the function of the ovarian cancer polypeptides are measured by examining parameters described above. A suitable physiological change that affects activity are used to assess the influence of a test compound on the polypeptides of this invention. When the functional consequences are determined using intact cells or animals, one can also measure a variety of effects such as, in the case of ovarian cancer associated with tumours, tumour growth, tumour metastasis, neovascularization, hormone release, transcriptional changes to both known and uncharacterized genetic markers (e.g., northern blots), changes in cell metabolism such as cell growth or pH changes, and changes in intracellular second messengers such as cGMP. In tire assays of the invention, mammalian ovarian cancer polypeptide is typically used, e.g., mouse, preferably human.

Assays to identify compounds with modulating activity are performed *in* vitro. For example, a ovarian cancer polypeptide is first contacted with a potential modulator and incubated for a suitable amount of time, e.g., from 0.5 to 48 hours. In one embodiment, the ovarian cancer polypeptide levels are determined *in vitro* by measuring the level of protein or mRNA. The level of protein is measured using immunoassays such as western blotting, ELISA and the like with an antibody that selectively binds to the ovarian cancer

polypeptide or a fragment thereof. For measurement of mRNA, amplification, e.g., using PCR, LCR, or hybridization assays, e.g., northern hybridization, RNAse protection, dot blotting, are preferred. The level of protein or mRNA is detected using directly or indirectly labeled detection agents, e.g., fluorescently or radioactively labeled nucleic acids, radioactively or enzymatically labeled antibodies, and the like, as described herein.

Alternatively, a reporter gene system are devised using the ovarian cancer-associated protein promoter operably linked to a reporter gene such as luciferase, green fluorescent protein, CAT, or (beta-gal. The reporter construct is typically transfected into a cell. After treatment with a potential modulator, the amount of reporter gene transcription, translation, or activity is measured according to standard techniques known to those of skill in the art.

In a preferred embodiment, as outlined above, screens are done on individual genes and gene products (proteins). That is, having identified a particular differentially expressed gene as important in a particular state, screening of modulators of the expression of the gene or the gene product itself are done. The gene products of differentially expressed genes are sometimes referred to herein as "ovarian cancer-associated proteins." The ovarian cancer-associated protein are a fragment, or alternatively, be the full length protein to a fragment shown herein.

In one embodiment, screening for modulators of expression of specific genes is performed. Typically, the expression of only one or a few genes are evaluated. In another embodiment, screens are designed to first find compounds that bind to differentially expressed proteins. These compounds are then evaluated for the ability to modulate differentially expressed activity. Moreover, once initial candidate compounds are identified, variants are further screened to better evaluate structure activity relationships.

In a preferred embodiment, binding assays are done. In general, purified or isolated gene product is used; that is, the gene products of one or more differentially expressed nucleic acids are made. For example, antibodies are generated to the protein gene products, and standard immunoassays are run to determine the amount of protein present. Alternatively, cells comprising the ovarian cancer-associated proteins are used in the assays.

Thus, in a preferred embodiment, the methods comprise combining a ovarian cancer-associated protein and a candidate compound, and determining the binding of the compound to the ovarian cancer-associated protein. Preferred embodiments utilize the human ovarian cancer-associated protein, although other mammalian proteins may also be used, e.g. for the development of animal models of human disease. In some embodiments, as outlined herein, variant or derivative ovarian cancer-associated proteins are used.

Generally, in a preferred embodiment of the methods herein, the ovarian cancer-associated protein or the candidate agent is non-diffusably bound to an insoluble support having isolated sample receiving areas (e.g. a microtiter plate, an array, etc.). The insoluble supports are made of any composition to which the compositions are bound, is readily separated from soluble material, and is otherwise compatible with the overall method of screening. The surface of such supports are solid or porous and of any convenient shape. Examples of suitable insoluble supports include microtiter plates, arrays, membranes and beads. These are typically made of glass, plastic (e.g., polystyrene), polysaccharides, nylon or nitrocellulose, teflon™, etc. microtitre plates and arrays are especially convenient because a large number of assays are carried out simultaneously, using small amounts of reagents and samples. The particular manner of binding of the composition is not crucial so long as it is compatible with the reagents and overall methods of the invention, maintains the activity of the composition and is nondiffusable. Preferred methods of binding include the use of antibodies (which do not sterically block either the ligand binding site or activation sequence when the protein is bound to the support), direct binding to "sticky" or ionic supports, chemical crosslinking, the synthesis of the protein or agent on the surface, etc. Following binding of the protein or agent, excess unbound material is removed by washing. The sample receiving areas may then be blocked through incubation with bovine serum albumin (BSA), casein or other innocuous protein or other moiety.

In a preferred embodiment, the ovarian cancer-associated protein is bound to the support, and a test compound is added to the assay. Alternatively, the candidate agent is bound to the support and the ovarian cancer-associated protein is added. Novel binding agents include specific antibodies, non-natural binding agents identified in screens of chemical libraries, peptide analogs, etc. Of particular interest are screening assays for agents that have a low toxicity for human cells. A wide variety of assays are used for this purpose, including labeled in vitro protein-protein binding assays, electrophoretic mobility

shift assays, immunoassays for protein binding, functional assays (phosphorylation assays, etc.) and the like.

The determination of the binding of the test modulating compound to the ovarian cancer-associated protein are done in a number of ways. In a preferred embodiment, the compound is labeled, and binding determined directly, e.g., by attaching all or a portion of the ovarian cancer-associated protein to a solid support, adding a labeled candidate agent (e.g., a fluorescent label), washing off excess reagent, and determining whether the label is present on the solid support. Various blocking and washing steps are utilized as appropriate.

In some embodiments, only one of the components is labeled, e.g., the proteins (or proteinaceous candidate compounds) are labeled. Alternatively, more than one component are labeled with different labels, e.g., ^{125}I for the proteins and a fluorophor for the compound. Proximity reagents, e.g., quenching or energy transfer reagents are also useful.

In one embodiment, the binding of the test compound is determined by competitive binding assay. The competitor is a binding moiety known to bind to the target molecule (i.e., a ovarian cancer-associated protein), such as an antibody, peptide, binding partner, ligand, etc. Under certain circumstances, there are competitive binding between the compound and the binding moiety, with the binding moiety displacing the compound. In one embodiment, the test compound is labeled. Either the compound, or the competitor, or both, is added first to the protein for a time sufficient to allow binding, if present. Incubations are performed at a temperature which facilitates optimal activity, typically between 4 and 40°C. Incubation periods are typically optimized, e.g., to facilitate rapid high throughput screening. Typically between 0.1 and 1 hour will be sufficient. Excess reagent is generally removed or washed away. The second component is then added, and the presence or absence of the labeled component is followed, to indicate binding.

In a preferred embodiment, the competitor is added first, followed by the test compound. Displacement of the competitor is an indication that the test compound is binding to the ovarian cancer-associated protein and thus is capable of binding to, and potentially modulating, the activity of the ovarian cancer-associated protein. In this embodiment, either component are labeled. Thus, e.g., if the competitor is labeled, the presence of

label in the wash solution indicates displacement by the agent. Alternatively, if the test compound is labeled, the presence of the label on the support indicates displacement.

In an alternative preferred embodiment, the test compound is added first, with incubation and washing, followed by the competitor. The absence of binding by the competitor may indicate that the test compound is bound to the ovarian cancer-associated protein with a higher affinity. Thus, if the test compound is labeled, the presence of the label on the support, coupled with a lack of competitor binding, may indicate that the test compound is capable of binding to the ovarian cancer-associated protein.

In a preferred embodiment, the methods comprise differential screening to identity agents that are capable of modulating the activity of the ovarian cancer-associated proteins. In this embodiment, the methods comprise combining a ovarian cancer-associated protein and a competitor in a first sample. A second sample comprises a test compound, a ovarian cancer-associated protein, and a competitor. The binding of the competitor is determined for both samples, and a change, or difference in binding between the two samples indicates the presence of an agent capable of binding to the ovarian cancer-associated protein and potentially modulating its activity. That is, if the binding of the competitor is different in the second sample relative to the first sample, the agent is capable of binding to the ovarian cancer-associated protein.

Alternatively, differential screening is used to identify drug candidates that bind to the native ovarian cancer-associated protein, but cannot bind to modified ovarian cancer-associated proteins. The structure of the ovarian cancer-associated protein are modeled, and used in rational drug design to synthesize agents that interact with that site. Drug candidates that affect the activity of a ovarian cancer-associated protein are also identified by screening drugs for the ability to either enhance or reduce the activity of the protein.

Positive controls and negative controls are used in the assays. Preferably control and test samples are performed in at least triplicate to obtain statistically significant results. Incubation of all samples is for a time sufficient for the binding of the agent to the protein. Following incubation, samples are washed free of non-specifically bound material and the amount of bound, generally labeled agent determined. For example, where a radiolabel is employed, the samples are counted in a scintillation counter to determine the amount of bound compound.

A variety of other reagents are included in the screening assays. These include reagents like salts, neutral proteins, e.g. albumin, detergents, etc. which are used to facilitate optimal protein-protein binding and/or reduce non-specific or background interactions. Also reagents that otherwise improve the efficiency of the assay, such as protease inhibitors, nuclease inhibitors, anti-microbial agents, etc., are used. The mixture of components are added in an order that provides for the requisite binding.

In a preferred embodiment, the invention provides methods for screening for a compound capable of modulating the activity of a ovarian cancer-associated protein. The methods comprise adding a test compound, as defined above, to a cell comprising ovarian cancer-associated proteins. Preferred cell types include almost any cell. The cells contain a recombinant nucleic acid that encodes a ovarian cancer-associated protein. In a preferred embodiment, a library of candidate agents are tested on a plurality of cells.

In one aspect, the assays are evaluated in the presence or absence or previous or subsequent exposure of physiological signals, e.g. hormones, antibodies, peptides, antigens, cytokines, growth factors, action potentials, pharmacological agents including chemotherapeutics, radiation, carcinogenics, or other cells (i.e. cell-cell contacts). In another example, the determinations are determined at different stages of the cell cycle process.

In this way, compounds that modulate ovarian cancer agents are identified. Compounds with pharmacological activity are able to enhance or interfere with the activity of the ovarian cancer-associated protein. Once identified, similar structures are evaluated to identify critical structural feature of the compound.

In one embodiment, a method of inhibiting ovarian cancer cell division is provided. The method comprises administration of a ovarian cancer inhibitor. In another embodiment, a method of inhibiting ovarian cancer is provided. The method comprises administration of a ovarian cancer inhibitor. In a further embodiment, methods of treating cells or individuals with ovarian cancer are provided. The method comprises administration of a ovarian cancer inhibitor.

In one embodiment, a ovarian cancer inhibitor is an antibody as discussed above. In another embodiment, the ovarian cancer inhibitor is an antisense molecule.

A variety of cell growth, proliferation, and metastasis assays are known to those of skill in the art, as described below.

Soft agar growth or colony formation in suspension

Normal cells require a solid substrate to attach and grow. When the cells are transformed, they lose this phenotype and grow detached from the substrate. For example, transformed cells can grow in stirred suspension culture or suspended in semi-solid media, such as semi-solid or soft agar. The transformed cells, when transfected with tumour suppressor genes, regenerate normal phenotype and require a solid substrate to attach and grow. Soft agar growth or colony formation in suspension assays are used to identify modulators of ovarian cancer sequences, which when expressed in host cells, inhibit abnormal cellular proliferation and transformation. A therapeutic compound would reduce or eliminate the host cells' ability to grow in stirred suspension culture or suspended in semisolid media, such as semi-solid or soft.

Techniques for soft agar growth or colony formation in suspension assays are described in Freshney, *Culture of Animal Cells a Manual of Basic Technique* (3rd ed., 1994), herein incorporated by reference. *See also,* the methods section of Garkavtsev *et al.* (I996), supra, herein incorporated by reference.

Contact inhibition and density limitation of growth

Normal cells typically grow in a flat and organized pattern in a petri dish until they touch other cells. When the cells touch one another, they are contact inhibited and stop growing. When cells are transformed, however, the cells are not contact inhibited and continue to grow to high densities in disorganized foci. Thus, the transformed cells grow to a higher saturation density than normal cells. This are detected morphologically by the formation of a disoriented monolayer of cells or rounded cells in foci within the regular pattern of normal surrounding cells. Alternatively, labeling index with (^{3}H)-thymidine at saturation density are used to measure density limitation of growth. *See* Freshney (1994), supra. The transformed cells, when transfected with tumour suppressor genes, regenerate a normal phenotype and become contact inhibited and would grow to a lower density.

In this assay, labeling index with (^{3}H)-thymidine at saturation density is a preferred method of measuring density limitation of growth. Transformed host cells are transfected

with a ovarian cancer-associated sequence and are grown for 24 hours at saturation density in non-limiting medium conditions. The percentage of cells labeling with (^{3}H)-thymidine is determined autoradiographically. *See,* Freshney (1994), supra.

Growth factor or serum dependence

Transformed cells have a lower serum dependence than their normal counterparts *(see, e.g.,* Temin, J. *Natl. Cancer Insti. 37:167-175 (1966);* Eagle *et al., J. Exp. Med. 131:836-879 (1970));* Freshney, *supra.* This is in part due to release of various growth factors by the transformed cells. Growth factor or serum dependence of transformed host cells are compared with that of control. *Tumor specific markers levels* Tumor cells release an increased amount of certain factors (hereinafter "tumour specific markers") than their normal counterparts. For example, plasminogen activator (PA) is released from human glioma at a higher level than from normal brain cells *(see, e.g.,* Gullino, *Angiogenesis, tumour vascularization, and potential interference with tumour growth.* in *Biological Responses in Cancer, pp. 178-184* (Mihich (ed.) *1985)).* Similarly, Tumor angiogenesis factor (TAF) is released at a higher level in tumour cells than their normal counterparts. *See, e.g.,* Folkman, *Angiogenesis and Cancer, Sem Cancer Biol. (1992)).* Various techniques which measure the release of these factors are described in Freshney *(1994), supra.* Also, *see,* Unkless *et al.* , *J. Biol. Chem. 249:4295-4305 (1974);* Strickland & Beers, J. *Biol. Chem. 251:5694-5702 (1976);* Whur *et al., Br. J. Cancer 42:305 312 (1980);* Gullino, *Angiogenesis, tumour vascularization, and potential interference with tumour growth.* in *Biological Responses in Cancer, pp. 178-184* (Mihich (ed.) *1985);* Freshney *Anticancer Res. 5:111-130 (1985).*

Invasiveness into Matrigel

The degree of invasiveness into Matrigel-or some other extracellular matrix constituent are used as an assay to identify compounds that modulate ovarian cancer-associated sequences. Tumor cells exhibit a good correlation between malignancy and invasiveness of cells into Matrigel or some other extracellular matrix constituent. In this assay, tumourigenic cells are typically used as host cells. Expression of a tumour suppressor gene in these host cells would decrease invasiveness of the host cells.

Techniques described in Freshney *(1994), supra,* are used. Briefly, the level of invasion of host cells are measured by using filters coated with Matrigel or some other extracellular matrix constituent. Penetration into the gel, or through to the distal side of the filter, is rated as invasiveness, and rated histologically by number of cells and

distance moved, or by prelabeling the cells with 125 1 and counting the radioactivity on the distal side of the filter or bottom of the dish. *See, e.g.*, Freshney *(1984), supra.*

Tumor growth in vivo

Effects of ovarian cancer-associated sequences on cell growth are tested in transgenic or immune-suppressed mice. Knock-out transgenic mice are made, in which the ovarian cancer gene is disrupted or in which a ovarian cancer gene is inserted. Knock- out transgenic mice are made by insertion of a marker gene or other heterologous gene into the endogenous ovarian cancer gene site in the mouse genome via homologous recombination. Such mice can also be made by substituting the endogenous ovarian cancer gene with a mutated version of the ovarian cancer gene, or by mutating the endogenous ovarian cancer gene, e.g., by exposure to carcinogens.

A DNA construct is introduced into the nuclei of embryonic stem cells. Cells containing the newly engineered genetic lesion are injected into a host mouse embryo, which is re-implanted into a recipient female. Some of these embryos develop into chimeric mice that possess germ cells partially derived from the mutant cell line. Therefore, by breeding the chimeric mice it is possible to obtain a new line of mice containing the introduced genetic lesion *(see, e.g.,* Capecchi *et al., Science 244:1288 (1989)).* Chimeric targeted mice are derived according to Hogan *et al., Manipulating the Mouse Embryo: A Laboratory Manual,* Cold Spring Harbor Laboratory *(1988)* and *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach,* Robertson, ed., IRL Press, Washington, *D.C., (1987).*

Alternatively, various immune-suppressed or immune-deficient host animals are used. For example, genetically athymic "nude" mouse *(see, e.g.,* Giovanella *et al., J. Natl. Cancer Inst. 52:921 (1974)),* a SCID mouse, a thymectomized mouse, or an irradiated mouse *(see, e.g.,* Bradley *et al., Br. J. Cancer 38:263 (1978);* Selby *et al., Br. J. Cancer 41:52 (1980))* are used as a host. Transplantable tumour cells (typically about 10^6 cells) injected into isogenic hosts will produce invasive tumours in a high proportions of cases, while normal cells of similar origin will not. In hosts which developed invasive tumours, cells expressing a ovarian cancer-associated sequences are injected subcutaneously. After a suitable length of time, preferably 4 to 8 weeks, tumour growth is measured (e.g. by volume or by its two largest dimensions) and compared to the control. Tumours that have a statistically significant reduction (using, e.g. Student's T test) are said to have inhibited growth.

Administration

therapeutic reagents of the invention are administered to patients, therapeutically. Typically, such proteins/polynucleotides and substances may preferably be combined with various components to produce compositions of the invention. Preferably the compositions are combined with a pharmaceutically acceptable carrier or diluent to produce a pharmaceutical composition (which are for human or animal use). Suitable carriers and diluents include isotonic saline solutions, for example phosphate-buffered saline. The composition of the invention are administered by direct injection. The composition are formulated for parenteral, intramuscular, intravenous, subcutaneous, intraocular, oral, vaginal or transdermal administration. Typically, each protein are administered at a dose of from 0.01 to 30 mg/kg body weight, preferably from 0.1 to 10 mg/kg, more preferably from 0.1 to 1 mg/kg body weight.

Polynucleotides/vectors encoding polypeptide components for use in modulating the activity of the ovarian cancer-associated proteins/polynucleotides are administered directly as a naked nucleic acid construct. When the polynucleotides/vectors are administered as a naked nucleic acid, the amount of nucleic acid administered may typically be in the range of from 1 μg to 10 mg, preferably from 100 μg to 1 mg.

Uptake of naked nucleic acid constructs by mammalian cells is enhanced by several known transfection techniques for example those including the use of transfection agents. Example of these agents include cationic agents (for example calcium phosphate and DEAE-dextran) and lipofectants (for example lipofectam™ and transfectam™). Typically, nucleic acid constructs are mixed with the transfection agent to produce a composition.

Preferably the polynucleotide or vector of the invention is combined with a pharmaceutically acceptable carrier or diluent to produce a pharmaceutical composition. Suitable carriers and diluents include isotonic saline solutions, for example phosphate-buffered saline. The composition are formulated for parenteral, intramuscular, intravenous, subcutaneous, oral, intraocular or transdermal administration.

The pharmaceutical compositions are administered in a range of unit dosage forms depending on the method of administration. For example, unit dosage forms suitable for oral administration include, powder, tablets, pills, capsules and lozenges. Orally

administered dosage forms will typically be formulated to protect the active ingredient from digestion and may therefore be complexed with appropriate carrier molecules and/or packaged in an appropriately resistant carrier. Suitable carrier molecules and packaging materials/barrier materials are known in the art.

The compositions of the invention are administered for therapeutic or prophylatic treatments. In therapeutic applications, compositions are administered to a patient suffering from a disease (e.g. ovarian cancer) in an amount sufficient to cure or at least partially ameliorate the disease and its complications. An amount adequate to accomplish this is defined as a "therapeutically effective dose". An amount of the composition that is capable of preventing or slowing the development of cancer in a patient is referred to as a "prophylactically effective dose".

The routes of administration and dosages described are intended only as a guide since a skilled practitioner will be able to determine readily the optimum route of administration and dosage for any particular patient and condition.

The present invention is further described with reference to the accompanying drawings and the following non-limiting examples.

EXAMPLE 1

Gene expression profiling to identify differentially-expressed genes in ovarian cancer

1. Tissue Bank and Database

Tissue was collected from patients undergoing treatment at the GCC, we have established an Ovarian Cancer Tissue Bank and Clinical Database that currently holds data on over 400 cases treated at the GCC between 1986 and 2002. Tissue (currently 149 fresh/frozen and 292 archival fixed paraffin-embedded samples) was acquired from patients undergoing cytoreductive surgery and does not interfere with the collection of tissue for the normal processing of diagnostic specimens. Patient consent, included in all our studies, was collected prior to surgery. Tissue specimens and their associated pathology reports were coded in order to maintain patient confidentiality. Uncoded data was electronically and/or physically locked with restricted access by appropriate senior investigators only. Clinical (diagnosis, treatment, residual disease) and pathological data (tumour grade, stage) were collected and updated (disease recurrence, patient survival) at regular intervals. This study has ethical approval from the South Eastern Sydney Area Health Service Research Ethics Committee, Australia. Clinical data and tissue collection are ongoing.

2. Genetic profiling of ovarian cancers

In order to identify those genes differentially regulated in epithelial ovarian cancer 51 ovarian cancer tumor samples were manually dissected from biological samples derived from subjects undergoing cytoreductive surgery. These samples comprised 8 endometrioid tumors, 4 mucinous tumors and 31 serous epithelial ovarian tumors, 12 corresponding omental deposits and 8 borderline (low-malignant potential) tumors.

RNA was isolated from the tumor samples in addition to 4 normal ovary samples using Trizol reagent (Life Technologies, Rockville, MD, USA) essentially according to manufacturer's instructions. RNA was then reverse transcribed using an oligo(dT) anchored oligonucleotide that additionally comprised a T7 promoter sequence. Isolated cDNA was then transcribed *in vitro* using the T7 MEGAscript kit (Ambion, Austin, TX, USA) according to manufacturer's instructions. Transcription was performed with biotinylated nucleotides (Bio-11-CTP and Bio-16-UTP) to enable detection of the transcribed cRNA.

Levels of gene expression in the cancer samples was then determined by analysing the transcribed cDNA samples using customized Affymetrix GeneChip® microarrays that

comprise 59,618 oligonucleotide probe sets. These probe sets facilitate analysis of 46,000 gene clusters, representing over 90% of the predicted expressed human genome.

Data were normalized, and changes in gene expression detected using a ranked penalized t-statistic with p-values adjusted for multiple testing using the Holm procedure. Analysis was performed using the LIMMA package (available from Bioconductor, Biostatistics Unit of the Dana Farber Cancer Institute at the Harvard Medical School/Harvard School of Public Health).

Gene expression in 186 samples representing 52 different tissues of the body was also determined using the previously described methods to facilitate the identification of changes in gene expression that are specific for ovarian cancer.

Using this method 284 up-regulated transcripts and 186 down-regulated transcripts were identified.

In order to determine the efficacy of such a method of analysis for determining gene expression changes associated with ovarian cancer, those genes identified were compared to results of published expression profile studies. Using this method, 71 genes were identified in the present study that had been previously identified, including, for example, genes known to be over-expressed in ovarian cancer, such as, for example MUC1 and E-cadherin.

The ovarian cancer-associated genes and proteins set forth in Table 1 include sequences that are up-regulated or down-regulated in ovarian cancer subjects, including subjects suffering specifically from serous, encodmetrioid, mucinous or clear cell ovarian cancer, or non-invasive (borderline) ovarian cancers of any phenotype, and subjects that suffered from recurrences of ovarian cancer in the medium term, or died within the medium term.

Data presented in Table 2 indicate those genes that are expressed at significantly higher levels or significantly reduced levels in patients suffering from serous cancer relative tot he level of expression of the same genes in a normal or healthy subject.

EXAMPLE 2

Validation of gene expression profiling results using tissue microarrays

Each of the transcripts identified as being differentially-expressed specifically in ovarian cancer was then further analysed using *in situ* hybridization or immunohistochemical staining of tissue microarrays constructed from a large cohort of primary ovarian tumor tissue. Such analysis confirms upregulation, down-regulation or total loss of expression of the transcripts identified in the microarray analysis of tumor samples.

Furthermore, as each of the samples in the tissue microarray have been clinicopathologically characterized (for example to identify cancer grade and/or disease stage) and the subjects from whom the tumors were isolated continuously monitored (to detect for example, death or relapse of cancer), changes with gene expression were also analysed for correlation with such parameters in order to determine predictive changes in gene expression.

The relative intensity and percentage of cells staining was determined and evaluated for associations with clinical stage and grade of disease and disease relapse using the Kaplan Meier method and log-rank test, and by univariate and bivariate analyses in a Cox proportional hazards model for gene expression and other clinical and pathologic predictors of outcome to determine the potential independent prognostic value of the markers being assessed.

Immunohistochemical analysis has been performed on several genes identified in gene profiling analysis of ovarian cancer samples. For example, SOX17, Ep-CAM and claudin 3 were shown by gene profiling analysis to be specifically up-regulated in ovarian cancer compared to normal ovaries (Figure 1 and Figure 2). Using immunohistochemical analysis, it was determined that SOX17, Ep-CAM and claudin 3 are upregulated in serous cancer, mucinous cancer, endometroid cancer and clear cell ovarian cancer.

Furthermore, immunohistochemical analysis has been used to analyse the expression of several other genes that are specifically upregulated in mucinous ovarian cancer. In particular the expression of LI-cadherin (cadherin 17), meprin alpha and Galectin 4 as detected using immunohistochemistry is shown in Figure 3. There was a significant increase in protein detected in the mucinous ovarian cancer samples compared to the normal ovary sample and serous ovarian cancer sample.

Immunohistochemical analysis was also performed to analyse the expression of three genes that are known to be upregulated in ovarian cancer (CA125, MUC-1 and E-cadherin) (Figures 1 and 2).

EXAMPLE 3

Identification of prognostic markers of ovarian cancer

Using a classical survival analysis to mine expression profiling data several genes that are associated with poor patient outcome (ie death or cancer relapse) have been identified (Tables 2 and 3). Such genes have clinical utility as prognostic indicators of disease..

Using detailed clinicopathological and postoperative data on all of the 51 patients included in our transcriptional profiling studies, including details of biochemical (eg. rising serum CA-125) and/or clinical recurrence of disease and overall survival, expression profiles were correlates with clinical parameters.

A preliminary survival analysis was performed on the 33 serous cancers within this cohort. The median follow-up time for these patients was 25.5 months from the date of primary laparotomy to the date of last follow-up or the date of death, and 21 of these patients (66%) were deceased from causes related to their malignancy.

Preliminary analysis of the expression profiles of these tumors identified several potential gene clusters that were associated with an increased risk of biochemical and clinical recurrence and overall survival, including the *EDD* gene (SEQ ID NO: 63). Exemplary prognostic markers for detecting ovarian cancer are shown in Tables 1 and 3. Preferred markers are indicated in Table 3.

Using immunohistochemical analysis two genes have been confirmed to be upregulated in serous ovarian cancer. In particular, sFRP4, a negative signalling protein of the Wnt pathway, and SOCS3, a negative signaller of IL-6 induced signalling are specifically upregulated in serous ovarian cancer when compared to normal ovarian tissue (Figure 4A).

Furthermore, using clinical patient data and correlating this information with gene expression levels using a Cox proportional hazards model, it has been shown that high

expression of sFRP4 correlates with a poor outcome in patients (n=127) with serous ovarian cancer (p=0.0056) (Figure 4B).

EXAMPLE 4

Validation of gene expression profiling results using quantitative RT-PCR

Candidate diagnostic genes are screened by quantitative RT-PCR against ovarian cancer cell lines to both validate the transcript profiling data (ie check their up- or down-regulation). Candidate diagnostic genes are screened using mRNA isolated from a panel of 9 ovarian tumour cell lines, (A2780, SKOV3, OVCAR-3, IGROV-1, CAOV3, OV-90, SW626, TOV-21G and TOV-112D), in addition to several other tumour cell lines including lines derived from breast, prostate and colorectal tumours, and immortalised (non-transformed) human ovarian surface epithelial cells and a primary normal breast epithelial cell line (184).

Total RNA is isolated from the normal and tumour cell lines, reverse transcribed into cDNA and used as template in a quantitative PCR using a LightCycler system (Roche Diagnostics). The relative amount of each gene product is determined by comparison to a standard housekeeping gene (GAPDH).

EXAMPLE 5

Identification of Novel Genes for Diagnosis of Ovarian Cancer

We identified candidate genes with diagnostic potential from our list of aberrantly regulated genes by applying the following selection procedure: genes with a good transcript profile and low p-value (ie highly significantly up- or down-regulated in ovarian cancer, as determined in Example 1); and mapping to areas of the genome that have been shown to be amplified or lost in ovarian cancer. Accordingly, it is likely that these genes are involved in the development and progression of ovarian cancer (ie putative oncogenes and tumour suppressor genes). Additional parameters for analysis included known or putative function in oncogenesis (eg signal transduction, regulation of cellular proliferation, apoptosis etc); and association with other forms of other tumours. Genes identified in this analysis are shown in Table 3.

One method for the diagnosis of cancer comprises detecting modified DNA shed by the developing tumour into the blood stream. This can include the detection of mutations in both oncogenes and tumour suppressor genes involved in the development and progression of ovarian cancer. Furthermore, it has been recently shown that aberrant

methylation of tumour suppressor genes, specifically hypermethylation of their gene promoters, frequently accompanies gene silencing in cancers, and indeed in some cases appears to be the predominant mechanism of gene silencing.

Combined with the knowledge of tumour nucleic acids circulating in the blood that reflect the biological characteristics of a tumour, the detection of methylation-specific tumour suppressor gene signatures for any given tumour type has promise as a specific and sensitive molecular test for detecting and monitoring cancer. Aberrant methylation is a frequent epigenetic event in epithelial ovarian cancer and many candidate tumour suppressor genes of epithelial ovarian cancer have been shown to be hypermethylated in epithelial ovarian cancer, such as, for example BRCA1.

In particular, expression of the candidate tumor suppressor gene MCC, has been shown to be down-regulated in epithelial ovarian cancer compared to normal ovarian tissue. MCC appears to be involved in critical cell growth regulatory processes and maps to a chromosomal region hypothesised as containing a tumor suppressor gene in ovarian cancer. Furthermore, we have identified a CpG island within the predicted promoter sequence of the MCC gene, a critical feature of genes that are subject to gene silencing by hypermethylation and a known characteristic of tumor suppressor genes. Taken together these data strongly implicate MCC as a candidate tumor suppressor gene involved in epithelial ovarian cancer.

Table 1
Genes having modified expression in subjects suffering from ovarian cancer

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
a. upregulated genes				
NM_002354	Hs.692:235	Ep-CAM; TACSTD1, tumor-associated calcium signal transducer 1; epithelial gylcoprotein	Lymphocyte antigen, plasma membrane, tumor antigen. Member of the GA733 family.C arcinoma-associated antigen expressed on most normal epithelial cells and gastrointestinal carcinomas and functions as a homotypic calcium-independent cell adhesion molecule. The antigen is being used as a target for immunotherapy treatment of human carcinomas.	0
BC006428	Hs.15093:210; Hs.290304:1	HSPC195, hypothetical protein HSPC195	Homo sapiens cDNA FLJ10920 fis, clone OVARC1000384-resourcerer.	0
NM_017697	Hs.24743:94	FLJ20171, hypothetical protein FLJ20171	contains 3 RNA recognition motifs	0
AW419196	Hs.257924:13	FLJ13782, Hypothetical protein FLJ13782	weakly similar to a drosophila transcription factor	0
AW630088	Hs.76550:164	MAL2	Mal2 T-cell differentiation protein; found thru interaction with TPD52 which is overexpressed in breast cancer; 4 TM are involved in vesicle transport	0
NM_004360	Hs.194657:233	CDH1, cadherin 1, type 1, E-cadherin (epithelial)	Tumor suppressor. Ca2+-dependent glycoprotein, mediates cell-cell interactions in epithelial cells. Mutations correlated with gastric, breast, colorectal, thyroid and ovarian cancer. Loss of function thought to contribute to progression in cancer by increasing proliferation, invasion, and/or metastasis. The ectodomain of this protein mediates bacterial adhesion to mammalian cells and the cytoplasmic domain is required for internalization.	0
NM_003761	Hs.172684:89	VAMP8, vesicle-associated membrane protein 8 (endobrevin)	Early endosome, membrane fraction, non-selective vesicle docking, non-selective vesicle transport, protein complex assembly, synaptic vesicle. Member of a family involved in docking or fusion of synaptic vesicles. Associated with the perinuclear vesicular structures of the early endocytic compartment.	0
NM_004415	Hs.349499	DSP, desmoplakin (DPI, DPII)	Cell shape and cell size control, cell-cell adherens junction, epidermal differentiation, intermediate filament, structural constituent of cytoskeleton. Acts as a site of attachment for intermediate filaments in desmosomes (intercellular junction in vertebrate epithelial cells). Compound heterozygosity for non-sense and mis-sense mutations underlies skin fragility/woolly hair syndrome.	0
NM_013230	Hs.286124:357; Hs.375108	CD24: CD24 antigen (small cell lung carcinoma cluster 4 antigen)	Plasma membrane, humoral defense mechanism. Cell surface antigen; glycosyl phosphatidylinositol (GPI)-linked glycoprotein that differentiates and activates granulocytes and B lymphocytes.	0

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
NM_003710	Hs.233950:84,Hs.182265:2,Hs.7771:1	SPINT1, serine protease inhibitor, Kunitz type 1. Hepatocyte growth factor activator inhibitor.	Extracellular, membrane fraction, serine protease inhibitor. Member of the Kunitz family of serine protease inhibitors. Hepatocyte growth factor activator inhibitor is a potent inhibitor specific for HGF activator and is thought to be involved in regulation of proteolytic activation of HGF in injured tissues.	0
NM_153345	Hs.17558:16	FLJ90586, hypothetical protein	Function unknown	0.0001
NM_015238	Hs.21543:36	KIAA0869, KIAA0869 protein; KIBRA	Function unknown	0.0002
AI282759	Hs.242463:1	KRT8, keratin 8	Cell structure, Cytoskeletal. May form intermediate filaments; type II keratin, member of a family of structural proteins. Disruption of mechanisms that normally regulate keratin expression in vivo could be related to inflammatory and neoplastic pancreatic disorders (Casanova 1999).	0.0002
AI393742	Hs.199067:46	ERBB3, v-erb-b2 erythroblastic leukemia viral oncogene homolog 3 (avian)	Transmembrane receptor protein tyrosine kinase, epidermal growth factor receptor, integral plasma membrane protein, protein amino acid phosphorylation. Member of the ERBB gene family of receptor tyrosine kinases, elevated levels in certain human mammary tumor cell lines. A receptor for heregulin, capable of mediating HGL-stimulated tyrosine phosphorylation of itself. Epidermal growth factor contains both positive and negative determinants for interaction with ErbB-2/ErbB-3 heterodimers (Stortelers 2002)	0.0002
AW957300	Hs.294142:167	ESTs, Weakly similar to CYL1_HUMAN CYLICIN I [H.sapiens]	Function unknown	0.0002
NM_012474; W70171	Hs.75939:33,Hs.170864:1	UMPK, uridine monophosphate kinase	Catalyzes the phosphorylation of uridine monophosphate to uridine diphosphate. First step in production of pyrimidine nucleoside triphosphates required for RNA and DNA synthesis. An allele of this gene may play a role in mediating nonhumoral immunity to Hemophilus influenzae type B.	0.0003
AA165082	Hs.146388:47,Hs.113919:3	MAP7, microtubule-associated protein 7	Establishment and/or maintenance of cell polarity, microtubule associated protein, microtubule cytoskeleton organization and biogenesis, structural molecule. Predominantly expressed in cells of epithelial origin. Involved in microtubule dynamics and cell polarization and differentiation. Stabilizes microtubules, and may modulate microtubule functions. Studies of the related mouse protein suggest an essential role in microtubule function required for spermatogenesis.	0.0004
AA284679	Hs.25640:264,Hs.5372:2	CLDN3, claudin 3	Integral plasma membrane protein, pathogenesis, tight junction, transmembrane receptor. Member of the claudin family of integral membrane proteins; receptor for Clostridium perfringens enterotoxin;	0.0004

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
NM_004433	Hs.166096:170	ELF3, E74-like factor 3 (ets domain transcription factor, epithelial-specific)	Embryogenesis and morphogenesis, transcription co-activator, transcription factor, transcription from Pol II promoter. ETS domain transcriptional activator; activates expression of epithelial cell specific genes.	0.0004
AW247252	Hs.75514:181	NP, nucleoside phosphorylase	DNA modification, nucleobase nucleoside nucleotide and nucleic acid metabolism, purine-nucleoside phosphorylase. Enzyme purine nucleoside phosphorylase together with adenosine deaminase (ADA) serves a key role in purine catabolism, referred to as the salvage pathway. Mutations in either enzyme result in a severe combined immunodeficiency (SCID).	0.0004
NM_015925	Hs.361379, Hs.95697:59,Hs.93649:1	LISCH7, Liver-specific bHLH-Zip transcription factor	LISCH protein	0.0004
NM_022454	Hs.97984:22	SOX17, SRY (sex determining region Y)-box 17	Likely ortholog of mouse SRY-box containing gene 17; alias SOX17	0.0005
AI124756	Hs.5337:191	IDH2, isocitrate dehydrogenase 2 (NADP+), mitochondrial	Carbohydrate metabolism, mitochondrion	0.0006
NM_003084	Hs.313:273,Hs.297895:1	SPP1, secreted phosphoprotein 1 (osteopontin, bone sialoprotein I, early T-lymphocyte activation 1)	Osteopontin (bone sialoprotein); bone and blood vessel extracellular matrix protein involved in calcification and atherosclerosis. Increased expression is associated with breast tumor metastasis (Urquidi 2002). Role in HCC, especially in cancer-stromal interactions (Gotoh 2002). Association between levels of a biomarker, osteopontin, and ovarian cancer suggest its clinical usefulness (Kim 2002).	0.0006
BE382756	Hs.169902:319,Hs.275406:1	SLC2A1, Solute carrier family 2 (facilitated glucose transporter), member 1	Glucose transporter, membrane fraction. SLC2A1/GLUT1 - facilitated glucose transporter. Glucose transporter is an integral membrane glycoprotein that is involved in transporting glucose into most cells. 12 TMs. Role in transport of glucose across the blood-brain barrier. Consistent marker of ovarian epithelial malignancy (Kalir 2002). Marker for discriminating hepatocellular carcinoma from other carcinomas (Zimmerman 2002).	0.0006
BE512730	Hs.65114:718,Hs.279437:1	KRT18, keratin 18	Cell shape and cell size control, embryogenesis and morphogenesis, intermediate filament, structural constituent of cytoskeleton. Component of intermediate filaments; type I epidermal keratin, strongly similar to murine Endo B. Expressed in single layer epithelial tissues of the body. Mutations linked to cryptogenic cirrhosis.	0.0006

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
NM_001769	Hs.1244:227,Hs.230559:1,Hs.242020:1	CD9: CD9 antigen (p24)	Plasma membrane, integral plasma membrane protein. Member of the transmembrane 4 superfamily (TM4SF); may mediate platelet activation and aggregation. Cell surface glycoprotein that is known to complex with integrins and other transmembrane 4 superfamily proteins.	0.0006
AI791905; NM_019027	Hs.95549:147,Hs.229556:1	FLJ20273, RNA-binding protein	Contains four RNA recognition motifs (RRM, RBD, or RNP)	0.0007
NM_006103	Hs.2719:108,Hs.54451:1	WFDC2, WAP four-disulfide core domain 2	Endopeptidase inhibitor, extracellular space, proteolysis and peptidolysis, spermatogenesis. Epididymis-specific secreted protein; may have a role in sperm maturation; arelong to a family of extracellular proteinase inhibitors. Expressed in pulmonary epithelial cells, and also expressed in some ovarian cancers.	0.0009
U81961	Hs.438580	SCNN1A, sodium channel, nonvoltage-gated 1 alpha	Amiloride-sensitive sodium channel, excretion, integral plasma membrane protein, membrane fraction, sodium transport. Alpha subunit of the amiloride-sensitive epithelial sodium channel; functions in nonvoltage-gated channel	0.0009
X69699; NM_013952	Hs.73149:72,Hs.213008:1	PAX8, paired box gene 8	Histogenesis and organogenesis, embryogenesis and morphogenesis, thyroid-stimulating hormone receptor, transcription factor. Member of the paired domain family of nuclear transcription factors; are involved in the ribosome assembly, required for normal thyroid development. PAX genes play critical roles during fetal development and cancer growth.	0.0009
AI027643	Hs.120912:12	ESTs	Function unknown	0.001
AA173992	Hs.7956:28	ESTs	Function unknown	0.0011
AB018249	Hs.10458:10	SCYA16, small inducible cytokine subfamily A (Cys-Cys), member 16.	Antimicrobial humoral response (sensu Invertebrata), cell-cell signaling, chemokine chemotaxis. Cytokine A16; lymphocyte and monocyte chemoattractant.	0.0011
NM_014791	Hs.184339:27	MELK, likely ortholog of maternal embryonic leucine zipper kinase.	KIAA0175 gene product; serine/threonine protein kinase domain	0.0011
NM_030674	Hs.18272:81	SLC38A1, solute carrier family 38, member 1	amino acid transporter A1 (ATA1), likely ortholog of mouse N-system amino acid transporter protein NAT2.	0.0012
NM_005682	Hs.6527:201	GPR56, G protein-coupled receptor 56	cell adhesion, cell-cell signalling, G-protein linked receptor, integral plasma membrane protein, G-protein linked receptor protein signalling pathway. Member of the G protein-coupled receptor family; similar to secretin and calcitonin receptors. 7 transmembrane domains, a mucin-like domain and cysteine box in the N-terminal region. Expressed in range of tissues, highest levels in thyroid, selectively within the monolayer of cuboidal epithelial cells of the smaller, more actively secreting follicles of human thyroid. Differentially expressed in melanoma cell lines with different	0.0012

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
			metastatic potential (Zendman et al 1999).	
AI669760	Hs.188881:6,Hs.199354:1	ESTs	dbEST Library Tissue Type restricted to prostate	0.0013
NM_001730	Hs.84728:127	KLF5, Kruppel-like factor 5 (intestinal)	RNA polymerase II transcription factor, transcription from Pol II promoter. Zinc finger transcriptional activator; localizes to the nucleus and binds the epidermal growth factor response element, binds GC boxes.	0.0014
AI355761	Hs.242463:2	KRT8, keratin 8	Cell structure, Cytoskeletal. May form intermediate filaments; type II keratin, member of a family of structural proteins. Disruption of mechanisms that normally regulate keratin expression in vivo could be related to inflammatory and neoplastic pancreatic disorders (Casanova 1999).	0.0014
BE019020	Hs.85838:171	SLC16A3, solute carrier family 16 (monocarboxylic acid transporters), member 3 (MCT3)	Integral plasma membrane protein, membrane fraction, monocarboxylic acid transport, monocarboxylic acid transporter. Member of monocarboxylate transporter family; may function as a transporter (MCT3).	0.0015
NM_001307	Hs.278562:101	CLDN7, claudin 7	Integral membrane protein, tight junction. Similar to murine Cldn7;	0.0016
NM_002266	Hs.159557:394	KPNA2, karyopherin alpha 2 (RAG cohort 1, importin alpha 1)	DNA metabolism, G2 phase of mitotic cell cycle. NLS-bearing substrate-nucleus import, cytoplasm, importin alpha-subunit, nuclear localization sequence binding, nucleoplasm, regulation of DNA recombination, spindle pole body and microtubule cycle (sensu Saccharomyces). Karyopherin alpha 2 (importin alpha 1); subunit of the NLS (nuclear localization signal) receptor. KPNA2 protein interacts with the NLSs of DNA helicase Q1 and SV40 T antigen and are involved in the nuclear transport of proteins. KPNA2 also may play a role in V(D)J recombination.	0.0016
AW176120	Hs.9061:77	MGC2477, hypothetical protein MGC2477	function unknown	0.0016
BE265489	Hs.3123:49	LLGL2, lethal giant larvae (Drosophila) homolog 2	Cytoskeleton, structural molecule. May associate with nonmuscle myosin II heavy chain. cDNA source cancer cell lines. 57% ID to m.musculus 1920362A tumor suppressor gene mgl1	0.0016
BE279383	Hs.26557:77	PKP3, plakophilin 3	Cell adhesion, intercellular junction. Desmosomal plaque proteins are members of the 'armadillo-repeat' multigene family and have important functions in cytoskeleton/cell membrane interactions.	0.0016

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
J05581; NM_002456	Hs.89603:128,Hs.296789:1	MUC1, mucin 1, transmembrane	Integral plasma membrane protein. Cell surface mucin glycoprotein expressed by most glandular and ductal epithelial cells and some hematopoietic cell lineages. Alterations in glycosylation in epithelial cancer cells. Marker for hepatocellular carcinoma. MUC1 metabolic complex conserved in tumor-derived and normal epithelial cells. Expression predictor of surgical outcome in mass-forming intrahepatic cholangiocarcinoma. Tyrosine kinase c-Src constitutes a bridge between cystic fibrosis transmembrane regulator channel failure and MUC1 overexpression in cystic fibrosis.	0.0016
AA531276	Hs.59509:9	ESTs (unnamed protein product)	Function unknown	0.0017
AW167128	Hs.231934:3	ESTs; weakly similar to A57717 transcription factor EC2	Function unknown	0.0018
AW368226	Hs.67928:25,Hs.229840:1	Ets-related transcription factor, ESX, epithelium-restricted Ets protein ESX-not in Unigene, but found using resourcerer.	Embryogenesis and morphogenesis, transcription co-activator, transcription factor, transcription from Pol II promoter.	0.0021
AK000733	Hs.23900:82	RACGAP1, Rac GTPase activating protein 1	Strongly similar to murine Racgap1 GTPase-activating protein for rac. The plexin-B1/Rac interaction inhibits PAK activation and enhances Sema4D ligand binding	0.0024
NM_014736	Hs.81892:95	KIAA0101 gene product	function unknown; no signficant hits with Superfamily	0.0025
NM_014586	Hs.109437:17	HUNK, hormonally upregulated neu tumor-associated kinase	Developmental processes, protein serine/threonine kinase, signal transduction, protein kinase containing SNF1 (fam of serine/threonine kinases) domain; progesterone and estradiol regulated. Similar to murine Hunk.	0.0025
AI885516	Hs.95612:31,Hs.251688:1	desmocollin type 2a, desmocollin 2, isoform Dsc2b preproprotein; desmosomal glycoprotein II/III; desmocollin-3-not in Unigene, but found using resourcerer.	Cell adhesion, intercellular junction	0.0027
AW194426	Hs.20726:17	ESTs	Function unknown	0.0027
NM_001982	Hs.199067:83,Hs.167386:1	ERBB3, HER3 (c-erb-B3), v-erb-b2 erythroblastic leukemia viral oncogene homolog 3 (avian)	Epidermal growth factor receptor, integral plasma membrane protein, protein amino acid phosphorylation. Member of the ERBB gene family of receptor tyrosine kinases, elevated levels in certain human mammary tumor cell lines. A receptor for heregulin, capable of mediating HGL-stimulated tyrosine phosphorylation of itself.	0.0028
NM_007019	Hs.93002:85	UBE2C, ubiquitin carrier protein E2-C	Ubiquitin-dependent protein degradation, degradation of cyclin, protein modification, positive control of cell proliferation. Subunit of a complex with ubiquitin ligase activity; complex that exhibits cyclin-selective ubiquitin ligase activity.	0.0031

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
BE184455	Hs.251754:128,Hs.245742:1	SLPI, secretory leukocyte protease inhibitor (antileukoproteinase)	Plasma protein, proteinase inhibitor. Secreted inhibitor which protects epithelial tissues from serine proteases. Found in various secretions including seminal plasma, cervical mucus, and bronchial secretions, has affinity for trypsin, leukocyte elastase, and cathepsin G. Its inhibitory effect contributes to the immune response by protecting epithelial surfaces from attack by endogenous proteolytic enzymes; the protein is also thought to have broad-spectrum anti-biotic activity.	0.0034
Y00815; NM_002840	Hs.75216:262,Hs.228792:1,Hs.245063:1	PTPRF, protein tyrosine phosphatase, receptor type, F	Cell adhesion, integral plasma membrane protein, transmembrane receptor protein, tyrosine phosphatase signaling pathway. Receptor-type protein tyrosine phosphatase F; interacts with the insulin receptor; has Ig-like and FN-III repeats in the extracellular domain	0.0035
AA706017	Hs.119944:14	ESTs	Function unknown	0.0038
AA256641	Hs.236894:24	ESTs, Highly similar to S02392 alpha-2-macroglobulin receptor precursor	Function unknown	0.0041
AW055308	Hs.31803:15	ESTs, Weakly similar to TRHY_HUMAN TRICHOHYALI [H.sapiens]	Function unknown	0.0043
AI301558	Hs.290801:35, Hs.356228	EST	Function unknown	0.0044
T18997	Hs.180372:119; Hs.394609	BCL2-like 1, Homo sapiens cDNA FLJ20750 fis, clone HEP05174 (hypothetical protein	Function unknown	0.0044
AI798863	Hs.87191:8	ESTs	Function unknown	0.0049
J03258	Hs.2062:146	VDR, vitamin D (1,25- dihydroxyvitamin D3) receptor	DNA binding, signal transduction, vitamin D3 receptor. Zinc-finger DNA-binding transcription factor. Genetic polymorphism determines bone mineral density. Stat1-vitamin D receptor interactions antagonize 1,25-dihydroxyvitamin D transcriptional activity and enhance stat1-mediated transcription.	0.0049
AA151647	Hs.68877:141,Hs.228686:1	CYBA, cytochrome b-245, alpha polypeptide	Cytochrome b, membrane, mitochondrion, superoxide metabolism. Alpha-subunit of cytochrome b245, primary component of the microbicidal oxidase system of phagocytes. CYBA deficiency is associated with chronic granulomatous disease (CGD).	0.005

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
AI538613	Hs.135657:8	TMPRSS3 Transmembrane protease, serine 3	Integral membrane protein, proteolysis and peptidolysis. Contains a serine protease domain, a transmembrane domain, a LDL receptor-like domain, and a scavenger receptor cysteine-rich domain. Serine proteases are known to be involved in a variety of biological processes, whose malfunction often leads to human diseases and disorders. Expressed in fetal cochlea and many other tissues, and is thought to be involved in the development and maintenance of the inner ear or the contents of the perilymph and endolymph. Missense mutations in autosomal recessive sensorineural deafness. Identified as a tumor associated gene that is overexpressed in ovarian tumors.	0.0051
NM_018000	Hs.79741:18	FLJ10116, hypothetical protein FLJ10116	Function unknown	0.0051
NM_144724	Hs.124740:18	hypothetical protein FLJ30532	59% identity to human Zinc finger protein 91	0.0051
AJ278016	Hs.55565:35	ANKRD3, ankyrin repeat domain 3	ATP binding, protein amino acid phosphorylation, protein binding, protein serine/threonine kinase.	0.0055
NM_013994	Hs.75562:147	DDR1, discoidin domain receptor family, member 1	Cell adhesion, integral plasma membrane protein, transmembrane receptor, protein tyrosine kinase. Epithelial-specific receptor protein tyrosine kinase; are involved in cell adhesion; has putative discoidin motifs in extracellular domain. DDR1 (CD167a) is a RTK that is widely expressed in normal and transformed epithelial cells and is activated by various types of collagen.	0.0055
T09997: NM_001312	Hs.70327:196,Hs.211478:1	CRIP-2, cysteine-rich protein 2	Zn-finger LIM domain protein;208-amino acid protein containing 2 LIM domains	0.0055
BE302796	Hs.105097:115	TK1, thymidine kinase 1, soluble	Cytoplasm, thymidine kinase. Generates thymidylate for DNA synthesis. TK1 gene expression together with TS, TP and DPD gene expression may play important roles in influencing the malignant behavior of epithelial ovarian cancer (Fujiwaki R 2002).	0.006
NM_001067	Hs.156346:184,Hs.270810:2	TOP2A, topoisomerase (DNA) II alpha (170kD)	DNA binding, DNA topoisomerase (ATP-hydrolyzing), nucleus. DNA topoisomerase II alpha; may relax DNA torsion upon replication or transcription. Involved in processes such as chromosome condensation, chromatid separation, and the relief of torsional stress that occurs during DNA transcription and replication. Catalyzes the transient breaking and rejoining of two strands of duplex DNA. The gene encoding this enzyme functions as the target for several anticancer agents and a variety of mutations in this gene have been associated with the development of drug resistance. Reduced activity of this enzyme may also play a role in ataxia-telangiectasia.	0.006

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
U46455	Hs.252189:148,Hs.248217:1	SDC4, syndecan 4 (amphiglycan, ryudocan)	Integral plasma membrane, proteoglycan syndecan. Syndecans are transmembrane heparan sulfate proteoglycans that appear to act as receptors or coreceptors involved in intracellular communication. Members of the MYC gene family and 4 members of the syndecan gene family are closely situated on 4 different chromosomes.	0.0061
M79141	Hs.13234:39	ESTs	Function unknown	0.0062
AI955040	Hs.301584:5,Hs.265398:3	ESTs, Moderately similar to hypothetical protein FLJ20378 [Homo sapiens] [H.sapiens]	Function unknown	0.0065
NM_005560	Hs.11669:81,Hs.231010:1	LAMA5, laminin, alpha 5	Basement lamina, structural molecule. Widely expressed in adult tissues, with highest levels in lung, heart, and kidney. Fifth member of the alpha subfamily of vertebrate laminin chains. Possible basement membrane protein; contains laminin EGF-like domain, two extracellular laminin G domains.	0.0066
BE563085	Hs.833:97	ISG15, interferon-stimulated protein, 15 kDa	Cell-cell signaling, cytoplasm, extracellular space, protein binding. Protein that is induced by interferon.	0.0068
BE278288	Hs.155048:119	LU, Lutheran blood group (Auberger b antigen included)	Blood group antigen, cell adhesion, integral plasma membrane protein, signal transduction, transmembrane receptor. Lutheran blood group glycoprotein; may play role in cell-cell, cell-matrix adhesion, signal transduction; member of the Ig superfamily, has integrin-binding motifs, SH3 domains.	0.0069
NM_020859	Hs.278628:52	ShrmL, Shroom-related protein (KIAA1481 protein)	Amiloride-sensitive sodium channel (weakly similar to Mus musculus PDZ domain actin binding protein)	0.0074
AI262789	Hs.93659:52	ERP70, protein disulfide isomerase related protein (calcium-binding protein, intestinal-related)	Endoplasmic reticulum lumen, protein secretion. Strongly similar to rat Rn.4070 (CABP2); may bind calcium.	0.008
NM_006147	Hs.11801:77	IRF6, interferon regulatory factor 6	Member 6 of the interferon regulatory factor transcription factor family; has low similarity to IRF4, which is a lymphocytic transcription factor that stimulates B cell proliferation.	0.0082
R61463	Hs.16165:50	LAK-4P, expressed in activated T/LAK lymphocytes	expressed in activated T/LAK lymphocytes	0.0082
AI878857; NM_016185	Hs.109706:285	HN1, hematological and neurological expressed 1 protein	Strongly similar to murine Hn1	0.0087
AK001783	Hs.73239:37	FLJ10901, hypothetical protein FLJ10901	B link shows some homology to KIAA1294 but no known function	0.009

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
AC004770	Hs.4756:99	FEN1, flap structure-specific endonuclease 1	DNA repair enzyme, DNA replication, UV protection, double-strand break repair, double-stranded DNA binding, double-stranded DNA specific exodeoxyribonuclease, endonuclease, fatty acid desaturation, membrane fraction. Removes 5' overhanging flaps in DNA repair and processes the 5' ends of Okazaki fragments in lagging strand DNA synthesis.	0.0093
AI567421	Hs.273330:137	AGRN: agrin	Agrin is a neuronal aggregating factor that induces the aggregation of acetylcholine receptors and other postsynaptic proteins on muscle fibers and is crucial for the formation of the neuromuscular junction. Acts at the nerve-muscle synapse in the glomerular basal membrane and on T-lymphocytes.	0.0093
AW161386	Hs.13561:49	MGC4692: hypothetical protein MGC4692	Function unknown	0.0103
M85430	Hs.155191:546	VIL2, villin 2 (ezrin)	Cytoskeletal anchoring, microvillus. Regulates cell adhesion and cortical morphogenesis. The cytoplasmic peripheral membrane protein encoded by this gene functions as a protein-tyrosine kinase substrate in microvilli. As a member of the ERM protein family, this protein serves as an intermediate between the plasma membrane and the actin cytoskeleton. It plays a key role in cell surface structure adhesion, migration, and organization.	0.0106
AW250380	Hs.109059:124,Hs.24756:11	MRPL12, mitochondrial ribosomal protein L12	Protein synthesis, General cellular role, Ribosomal subunit, Mitochondrial, RNA-binding protein, Ribosome-associated.	0.0114
AI733848; NM_021220	Hs.71935:13	ZNF339, zinc finger protein 339	Zinc finger protein	0.0115
AF111856; NM_006424	Hs.105039:48	SLC34A2, solute carrier family 34 (sodium phosphate), member 2	SLC34A2: solute carrier family 34 (sodium phosphate), member 2; contains 8 predicted TMs and a cysteine-rich N-terminal region. Type 2 sodium-dependent phosphate transporter. member of the renal type II co-transporter family.	0.0121
BE386983; NM_138410	Hs.343214	CKLFSF7; chemokine-like factor super family 7	chemokine-like factor gene superfamily; transmb 4 superfamily	0.0131
AA433988	Hs.98502:8	MUC16, mucin 16, CA125	Mucin 16. Alias CA125 ovarian cancer antigen	0.0137
AW248314	Hs.9622:83	MRPS18A, mitochondrial ribosomal protein S18A	Mitochondrial small ribosomal subunit, protein biosynthesis, structural constituent of ribosomeribosomal mitochondrial protein S18A	0.0149

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
AA454501	Hs.43666:65	PTP4A3, protein tyrosine phosphatase type IVA, member 3	Prenylated protein tyrosine phosphatase. PTPs are cell signaling molecules that play regulatory roles in a variety of cellular processes. Strong similarity to murine Ptp4a3 (Mm.4124). Overexpression of this gene in mammalian cells was reported to inhibit angiotensin-II induced cell calcium mobilization and promote cell growth. PRL3 (PTP4A3) expressed at high levels cancer metastases (Saha et al. 2001), PRL3 gene is important for colorectal cancer metastasis.	0.016
U33446	Hs.75799:116	PRSS8, protease, serine, 8 (prostasin)	Extracellular space, plasma membrane, serine type peptidase. A trypsinogen, member of the trypsin family of serine proteases. Highly expressed in prostate epithelia, one of several proteolytic enzymes found in seminal fluid. Protease-mediated regulation of sodium absorption is a function of human airway epithelia, and prostasin is a likely candidate for this activity.	0.0166
X98654	Hs.93837:43	PITPNM, phosphatidylinositol transfer protein, membrane-associated	Brain development, lipid metabolism, membrane fraction, phosphatidylinositol transporter, phototransduction. Catalyzes the transfer of phosphatidylinositol between membranes; similar to Drosophila rdgB.	0.0167
AI660149	Hs.44865:39,Hs.300819:19,Hs.293904:14	LEF1, Lymphoid enhancer-binding factor-1	Very strongly similar to murine Lef1; may act as a transcription factor. Expressed in pre-B and T cells. Binds to T-cell receptor-alpha enhancer and confers maximal enhancer activity. A target gene ectopically activated in colon cancer, from selective activation of a promoter for a full-length LEF1 isoform that binds beta-catenin (HOVANES 2001).	0.0172
AF098158; NM_012112	Hs.9329:152	C20orf1, chromosome 20 open reading frame 1	ATP binding, GTP binding, cell proliferation, mitosis, nucleus spindle. Proliferation-associated nuclear protein; associates with the spindle pole and mitotic spindle during mitosis	0.0183
AB014551	Hs.155120:101, Hs.337774	ARHGEF2, rho/rac guanine nucleotide exchange factor (GEF) 2	Cell shape and cell size control, cell surface receptor linked signal transduction, guanyl-nucleotide exchange factor, microtubule cytoskeleton. Rho GTPases play a fundamental role in numerous cellular processes that are initiated by extracellular stimuli that work through G protein coupled receptors. The encoded protein may form complex with G proteins and stimulate Rho-dependent signals. Rho/Rac guanine nucleotide exchange factor (GEF) 2; associates with microtubules, stimulates GTP binding on Rac and Rho	0.0206
AI278023	Hs.89986:24,Hs.290780:1	ESTs	Function unknown	0.0208

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
Z95152	Hs.178695:25,Hs.79107:1	MAPK13, *mitogen-activated protein kinase 13*	MAP kinase, antimicrobial humoral response (sensu Invertebrata), cell surface receptor, signal transduction, chemotaxis, stress response. MAP kinases act as an integration point for multiple biochemical signals, and are involved in a wide variety of cellular processes such as proliferation, differentiation, transcription regulation and development. Are activated by proinflammatory cytokines and cellular stress. Transcription factor ATF2, and microtubule dynamics regulator stathmin are substrates of this kinase.	0.0217
AW840171	Hs.265398:7	ESTs, Moderately similar to hypothetical protein FLJ20378 [Homo sapiens] [H.sapiens]	Function unknown	0.0222
D49441	Hs.155981:53	MSLN, mesothelin	Cell adhesion, cell surface antigen, membrane. Pre-pro-megakaryocyte potentiating factor. An antibody that reacts with ovarian cancers and mesotheliomas was used to isolate a cell surface antigen named mesothelin. Although the function of mesothelin is unknown, it may play a role in cellular adhesion and is present on mesothelium, mesotheliomas, and ovarian cancers.	0.0225
AW797437	Hs.69771:262,Hs.444:1,Hs.294163:1	EST, CM1-UM0039-030400-173-a09	Function unknown	0.0229
BE396290	Hs.5097:261	SYNGR2, synaptogyrin 2	Integral plasma membrane protein, member of a family of transmembrane synaptic vesicle proteins, specialized secretory organelles that store neurotransmitters in nerve terminals, and release them by fusing with the presynaptic plasma membrane during exocytosis.	0.0229
AI656166; NM_025080	Hs.7331	ASRGL1; asparaginase like 1	glycoprotein catabolism	0.02
NM_002145	Hs.2733:25	HOXB2, *homeo box B2, Hox2H protein*	Circulation, developmental processes, transcription factor. Member of homeodomain family of DNA binding proteins; may regulate gene expression, morphogenesis, and differentiation. Genes of the HOXB (or HOX2) complex are expressed specifically in erythromegakaryocytic cell lines, some are expressed only in hematopoietic progenitors.	0.024
AW959311	Hs.87019:8; Hs.172012	Hypothetical protein DKFZp434J037	probable serine/threonine protein kinase; KIAA0537	0.0251

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
NM_000269	Hs.118638:166,Hs.276104:1,Hs.276127:1,Hs.276246:1	NME1, non-metastatic cells 1, protein (NM23A)	Transcription factor and nucleoside diphosphate kinase; has a role in the transcriptional regulation of c-myc expression. Mutations in NME1 have been identified in aggressive neuroblastomas.	0.0257
AA379597	Hs.5199:87,Hs.277192:1	HSPC150, HSPC150 protein similar to ubiquitin-conjugating enzyme	Similar to ubiquitin conjugating enzyme	0.0259
BE148235	Hs.193063:100	Homo sapiens cDNA FLJ14201 fis, clone NT2RP3002955	high homology to ARP-3 actin-like protein	0.0259
AI683243; AI587638	Hs.97258	ESTs	Mod similarity to S29539 ribosomal protein L13a	0.03
AF111713	Hs.286218:64	JAM1, junctional adhesion molecule	Cell motility, inflammatory response, intercellular junction. Role in the regulation of tight junction assembly in epithelia. Ligation of JAM is required for reovirus-induced activation of NF-kappa-B and apoptosis. Role in lymphocyte homing.	0.0261
BE391635	Hs.75725:450,Hs.274751:1,Hs.277482:1,Hs.277468:1	TAGLN2, transgelin 2	Complex assembly protein. Homolog of the protein transgelin, which is one of the earliest markers of differentiated smooth muscle. Function not yet determined. Are an actin-binding protein.	0.0275
D14697	Hs.77393:201,Hs.247769:1	FDPS, farnesyl diphosphate synthase (farnesyl pyrophosphate synthetase, dimethylallyltranstransferase, geranyltranstransferase)	Farnesyl pyrophosphate synthetase (farnesyl diphosphate synthase); part of the cholesterol synthesis pathway.	0.0276
AW194364	Hs.94814	MGC2865, Hypothetical protein MGC2865	Function unknown.	0.0295
T47364	Hs.278613:145	IFI27, interferon, alpha-inducible protein 27	Integral membrane protein. Isolated from estradiol-treated human breast carcinoma cells. Induced by interferon-alpha in human cell lines of different origin, expression is independent of the presence of estradiol receptor in the cells.	0.03
U17760	Hs.301103:71,Hs.75517:24,Hs.199068:1	LAMB3, Laminin, beta 3 (nicein (125kD), kalinin (140kD), BM600 (125kD)) (Accn NM_000228)	Epidermal differentiation, laminin-5, structural molecule. Member of a family of basement membrane proteins. LAMB3 serves as the beta chain in laminin-5. Mutations in LAMB3 have been identified as the cause of various types of epidermolysis bullosa.	0.0304
AU076517	Hs.184276:142	SLC9A3R1, solute carrier family 9 (sodium/hydrogen exchanger), isoform 3 regulatory factor 1	Actin cytoskeleton, protein complex assembly. Regulatory cofactor of the NHE3 (SLC9A3) sodium/hydrogen antiporter; interacts with merlin (NF2) and ERM family members; has two PDZ domains. Structural determinants in interaction of beta 2 adrenergic and platelet-derived growth factor receptors	0.0312

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
AW880841	Hs.96908 , Hs.74427:112	PIG11 , p53-induced protein	Negative control of cell proliferation, stress response. May generate or respond to oxidative stress, may have a role in p53-dependent apoptosis Polyak K, Xia Y, Zweier JL, Kinzler KW, Vogelstein B. A model for p53-induced apoptosis.Nature. 1997 Sep 18;389(6648):300-5.	0.0314
H24185	Hs.92918:91	BM-009, hypothetical protein BM-009	Function unknown	0.0314
BE614410	Hs.23044:51	MGC16386, hypothetical protein, similar to RIKEN cDNA	Function unknown.	0.0326
H16423	Hs.82685:37	CD47: CD47 antigen (Rh-related antigen, integrin-associated signal transducer)	Oncogenesis, plasma membrane, plasma glycoprotein, cell-cell matrix adhesion, integral plasma membrane proteoglycan, integrin receptor signal signalling pathway. Similar to Rh-antigen; may interact with integrins and have a role in intracellular calcium increase during cell adhesion.	0.0336
AU076611; NM_006636	Hs.154672:123	MTHFD2, methylene tetrahydrofolate dehydrogenase (NAD+ dependent); methenyltetrahydrofolate cyclohydrolase	Electron transporter, methenyltetrahydrofolate cyclohydrolase, mitochondrion. encodes a nuclear-encoded mitochondrial bifunctional enzyme with methylenetetrahydrofolate dehydrogenase and methenyltetrahydrofolate cyclohydrolase activities. may provide formyltetrahydrofolate for formylmethionyl tRNA synthesis;.involved in initiation of mitochondrial protein synthesis.	0.0342
AI859390	Hs.288940:49	TMEM8, five-span transmembrane protein M83; type I transmembrane protein	Integral plasma membrane protein. Type I transmembrane protein; contains five membrane-spanning domains	0.0345
AA159216	Hs.55505:57	FLJ20442, hypothetical protein FLJ20442	Contains a dual specificity protein phosphatase catalytic domain; 34% similar to protein-tyrosine phosphatase	0.0354
AF119665; NM_021129	Hs.184011:156	PP, pyrophosphatase (inorganic)	Inorganic diphosphatase, phosphate metabolism. Catalyzes the hydrolysis of pyrophosphate to inorganic phosphate	0.0358
BE513613; NM_005720	Hs.11538:275	ARPC1B, actin related protein 2/3 complex, subunit 1A (41 kD)	Cell motility, structural constituent of cytoskeleton. Arp2/3 complex, subunit 1A; involved in assembly of the actin cytoskeleton, may have a role in protrusion of lamellipodia	0.0367
NM_012153	Hs.182339	EHF: ets homologous factor	DNA binding, tumor suppressor, cell proliferation, developmental processes, transcription activating factor. Member of the ESE subfamily of Ets transcription factors	0.0404
AW772298	Hs.21103:40,Hs.266784:2,Hs.102950:1	Homo sapiens mRNA; cDNA DKFZp564B076 (from clone DKFZp564B076)	Alias coat protein gamma-cop	0.0423
H16646	Hs.118666:66	PP591, hypothetical protein PP591	Hypothetical protein PP591 (Novel Human cDNA clones with function of inhibiting cancer cell growth; unpublished)	0.043

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
AA279661	Hs.83753:244,Hs.301236:3	SNRPB, small nuclear ribonucleoprotein polypeptides B and B1	Spliceosome, mRNA splicing, small nuclear ribonucleoprotein. U1 and U2 snRNP protein; component of snRNP complexes, required units of the spliceosome	0.0446
BE001596	Hs.85266:102	ITGB4, integrin, beta 4	Cell adhesion receptor, integrin, invasive growth, oncogenesis. Beta 4 subunit of integrin; involved in cell-cell and cell-matrix interactions; member of a family of cell-surface proteins. Binding of beta 4 to plectin is essential for the proper formation and function of hemidesmosomes.	0.0453
BE246444	Hs.283685:148,Hs.232028:2	FLJ20396, hypothetical protein FLJ20396	100%/175aa unnamed protein g7020468	0.0453
X54942	Hs.83758:34	CKS2, CDC28 protein kinase 2	Cell proliferation, regulation of CDK activity. Similar to S. pombe p13suc1; binds and regulates CDK-cyclin complexes. expressed in different patterns through the cell cycle in HeLa cells, which reflects specialized role for the encoded protein.	0.0478
AA305599	Hs.238205:36	PRO2013, hypothetical protein PRO2013	Function unknown	0.0483
AF019226	Hs.8036:84	RAB3D, member RAS oncogene family	RAB small monomeric GTPase, hemocyte development. GTP-binding protein; are involved in vesicle transport; member of the RAB family of small GTPases. Alias GOV, that is overexpressed in glioblastoma multiforme tissue as compared to normal brain tissue. GOV is also highly expressed in recurrent glioma, colon tumor metastatic to brain, breast tumors, prostate tumors, and several tumor cell lines	0.0485
NM_001949	Hs.1189:65,Hs.296939:2	E2F3, E2F transcription factor 3	Protein binding, transcription factor, transcription initiation from Pol II promoter. Involved in cell cycle regulation, binds retinoblastoma protein (Rb). E2F family plays a crucial role in the control of cell cycle and action of tumor suppressor proteins and is also a target of the transforming proteins of small DNA tumor viruses.	0.049
AF217513	Hs.279905:73,Hs.283649:4	ANKT, nucleolar protein ANKT	clone HQ0310 PRO0310p1 nucleolar protein ANKT - no functional data	0.0504
AW513143	Hs.98367:8	ESTs	Expressed in uterus	0.0535
AJ245671	Hs.12844:73	EGFL6, EGF-like-domain; multiple 6	Cell cycle, oncogenesis, integrin ligand, extracellular space. Member of the epidermal growth factor (EGF) repeat superfamily; contains an EGF-like-domain. Expressed early during development, and its expression has been detected in lung and meningioma tumors.	0.0568
AA084248	Hs.85339:64	GPR39, G protein-coupled receptor 39	G-protein linked receptor, G-protein coupled receptor protein signaling pathway, integral plasma membrane protein.	0.19

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
U62801	Hs.79361:65	KLK6, kallikrein 6 (neurosin, zyme)	Serine type peptidase, pathogenesis. Neurosin (protease M, zyme); a serine protease that cleaves amyloid precursor protein (APP). Growing evidence suggests that many kallikreins are implicated in carcinogenesis and some have potential as novel cancer and other disease biomarkers.	0.0159
D49441	Hs.155981:53	MSLN, mesothelin	Cell adhesion, cell surface antigen, membrane. Pre-pro-megakaryocyte potentiating factor. An antibody that reacts with ovarian cancers and mesotheliomas was used to isolate a cell surface antigen named mesothelin. Although the function of mesothelin is unknown, it may play a role in cellular adhesion and is present on mesothelium, mesotheliomas, and ovarian cancers.	0.147
X51630	Hs.1145:22,Hs.29685 1:1	WT1, Wilms tumor 1	Nucleus, transcription factor, transcription regulation. 4 Zn finger domains. Functions in kidney and gonad proliferation and differentiation. Mutations in this gene are associated with the development of Wilms tumors in the kidney or with abnormalities of the genitourinary tract.	0.2938
AB018305	Hs.5378:149	SPON1, spondin 1, (f-spondin) extracellular matrix protein	Extracellular matrix protein. Very strongly similar to rat F-spondin (Rn.7546); may have a role in the growth and guidance of axons.	0.3394
AA433988	Hs.98502:8	MUC16, mucin 16, CA125	Mucin 16. Alias CA125 ovarian cancer antigen	0.6568
NM_006149	Hs.5302:132	LGALS4, lectin, galactoside-binding, soluble, 4 (galectin 4)	Lectin, cytosol, cell adhesion, plasma membrane. Binds to beta galactoside, involved in cell adhesion, cell growth regulation, inflammation, immunomodulation, apoptosis and metastasis; member of a family of lectins. LGALS4 is an S-type lectin that is strongly underexpressed in colorectal cancer.	0.0001
AA315933	Hs.120879:17	Homo sapiens, clone MGC:32871 IMAGE:4733535, mRNA, complete cds	Function unknown	0.0001
U47732	Hs.84072:110	TM4SF3, transmembrane 4 superfamily member 3	Integral plasma membrane protein, lysosome, pathogenesis, protein amino acid glycosylation, signal transducer, tumor antigen. Cell surface glycoprotein defined by the monoclonal antibody CO-029 is a 27- to 34-kD membrane protein expressed in gastric, colon, rectal, and pancreatic carcinomas but not in most normal tissues	0.0028

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
NM_005588	Hs.179704	MEP1A, meprin A alpha, PABA peptide hydrolase	metalloprotease located apically and secreted by epithelial cells in normal colon; degrades broad range of ECM components in vitro; proposed role in tumour progression by facilitating migration, intravasation and metastasis	0.01
AW503395	Hs.5541:112	ATP2A3, ATPase, Ca++ transporting, ubiquitous	Endoplasmic reticulum, adenosinetriphosphatase, small molecule transport, calcium-transporting ATPase, integral plasma membrane protein. Sarco/endoplasmic reticulum Ca2+-ATPase; pumps calcium.	0.0154
NM_004063	Hs.89436:50	CDH17, cadherin 17, LI cadherin (liver-intestine)	Cell adhesion, integral plasma membrane protein, membrane fraction, small molecule transport, transporter. Member of the cadherin family of calcium-dependent glycoproteins; facilitates uptake of peptide-based drugs, may mediate cell-cell interactions. Component of the gastrointestinal tract and pancreatic ducts, intestinal proton-dependent peptide transporter in the first step in oral absorption of many medically important peptide-based drugs.	0.0172
AI073913	Hs.100686:20	LOC155465, anterior gradient protein 3	Oncogenesis	0.0266
AI928445	Hs.92254:80	SYTL2: synaptotagmin-like 2	Synaptotagmin-like protein of the C2 domain-containing family of proteins. Although the specific function of the synaptotagmin-like proteins is unknown, a role in regulation of synaptic vesicle trafficking via their C2 domains has been suggested. Region of weak similarity to murine Gph	0.08
W40460	Hs.144442:5	PLA2G10: phospholipase A2, group X	Extracellular, secreted phospholipase A2. Group X secretory phospholipase_a2; hydrolyzes the phospholipid sn-2 ester bond; member of the phospholipase family	0.1888
AA132961	Hs.212533:4	Homo sapiens cDNA: FLJ22572 fis, clone HSI02313	Function unknown	0.1965
AF111856	Hs.105039:48	SLC34A2, solute carrier family 34 (sodium phosphate), member 2	SLC34A2: solute carrier family 34 (sodium phosphate), member 2; contains 8 predicted TMs and a cysteine-rich N-terminal region. Type 2 sodium-dependent phosphate transporter. member of the renal type II co-transporter family.	0.5078
AA143654		zo65a02.r1 Stratagene pancreas (#937208) Homo sapiens cDNA clone IMAGE:591722 5', mRNA sequence	Function unknown	0.036

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
b. prognostic indicators				
AA046217	Hs.105370:2	ESTs	Function unknown	0.00
NM_015902		EDD:Homo sapiens progestin induced protein (DD5), mRNA. VERSION NM_020967.1 GI	Soluble fraction, cell proliferation, ubiquitin--protein ligase, ubiquitin conjugating enzyme, ubiquitin-dependent protein degradation. Member of the HECT family of proteins; may function as an E3 ubiquitin-protein ligase. This gene is localized to chromosome 8q22, a locus disrupted in a variety of cancers. This gene potentially has a role in regulation of cell proliferation or differentiation.	0.00
T83882	Hs.97927:20	ESTs	Function unknown	0.01
#(NOCAT)		NM_001615*:Homo sapiens actin, gamma 2, smooth muscle, enteric (ACTG2), mRNA. variant 1, mRNA.	Structural protein of muscle. Gamma 2 actin; enteric-type, smooth muscle cell actin.	0.01
AB040888		Homo sapiens mRNA for KIAA1455 protein, partial cds	Function unknown	0.01
AA628980	Hs.192371:3	DSCR8 down syndrome critical region protein DSCR8	Function unknown	0.01
AI623351	Hs.172148:51	ESTs	Function unknown	0.01
AW614420	Hs.204354:383	ARHB ras homolog gene family, member B	RHO small monomeric GTPase, RHO protein signal transduction, peripheral plasma membrane protein. Ras-related GTP binding protein of the rho subfamily, member B; may regulate assembly of actin stress fibers and focal adhesions; very strongly similar to murine Arhb.	0.01
AA243499	Hs.104800:23	hypothetical protein FLJ10134	Highly similar to murine p19.5; are a membrane protein	0.01
AF251237	Hs.112208:16	GAGED2 XAGE-1 protein	GAGE genes are expressed in a variety of tumors and in some fetal and reproductive tissues. This gene is strongly expressed in Ewing's sarcoma, alveolar rhabdomyosarcoma and normal testis. The protein encoded by this gene contains a nuclear localization signal and shares a sequence similarity with other GAGE/PAGE proteins. Because of the expression pattern and the sequence similarity, this protein also belongs to a family of CT (cancer-testis) antigens.	0.01
AI970797	Hs.64859:16	ESTs	Function unknown	0.01
AF145713	Hs.61490:51	SCHIP1 schwannomin-interacting protein 1	Cytoplasm. Associates with the neurofibromatosis type 2 protein schwannomin (NF2); contains a coiled-coil domain|Proteome	0.01

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
X78565	Hs.289114:173,Hs.74637:1	TNC hexabrachion (tenascin C, cytotactin)	Cell adhesion, extracellular matrix, cell adhesion receptor, ligand binding or carrier. Hexabrachion (tenascin c), an extracellular matrix glycoprotein; has epidermal growth factor-like repeats	0.01
T97307		gb:ye53h05.s1 Soares fetal liver spleen 1NFLS Homo sapiens cDNA clone IMAGE:121497 3', mRNA sequence.	Function unknown	0.01
BE243845	Hs.75511:418	CTGF connective tissue growth factor	Cell motility, plasma membrane, soluble fraction, response to wounding, extracellular matrix, extracellular space, epidermal differentiation, cell growth and maintenance, insulin-like growth factor binding, insulin-like growth factor receptor binding protein. Connective tissue growth factor; binds IGF, may have a role in regulating normal and neoplastic cell growth	0.01
AW068302	Hs.182183:214,Hs.325474:172,Hs.283080:7	CALD1 caldesmon 1	Cytoskeleton, actin binding, calmodulin binding, tropomyosin binding. Protein of unknown function. Actomyosin regulatory protein, non-muscle form	0.01
AL133561	Hs.241426:5	DKFZP434B061 protein	Function unknown	0.01
BE313555	Hs.7252:158	RAI17 retinoic acid induced 17	Function unknown	0.02
X07820	Hs.2258:1	MMP10 matrix metalloproteinase 10 (MMP10; stromelysin 2)	Zinc binding, extracellular space, extracellular matrix, metalloendopeptidase, proteolysis and peptidolysis. Stromelysin 2; matrix metalloprotease that degrades connective tissue	0.02
AI973016	Hs.15725:77	IER5 immediate early response 5	Function unknown. A related mouse gene may play an important role in mediating the cellular response to mitogenic signals.	0.02
AF084545		Homo sapiens versican Vint isoform, mRNA, partial cds	Function unknown	0.02
U41518	Hs.74602:146,Hs.767:1	AQP1 aquaporin 1 (channel-forming integral protein, 28kD)	Excretion, water transport, water transporter, integral plasma membrane protein. Aquaporin 1 (channel-forming integral protein); member of a family of water-transporters	0.02
Z11894		H.sapiens rearranged mRNA for immunoglobulin kappa chain (VNJ)		0.02
AW138190	Hs.180248:8	ZNF124 zinc finger protein 124 (HZF-16)	DNA binding. C2H2 zinc-finger protein 124	0.02
BE086548	Hs.42346:83,Hs.6975:42	MYOZ2 myozenin 2	calcineurin-binding protein calsarcin-1	0.02

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
W47196	Hs.166172:50	ARNT aryl hydrocarbon receptor nuclear translocator	Nucleus, transcription factor, transcription co-activator, transcription, DNA-dependent, protein-nucleus import, translocation, aryl hydrocarbon receptor nuclear translocator. Aryl hydrocarbon receptor nuclear translocator; used in receptor translocation from cytosol to nucleus	0.02
AI796870	Hs.54277:76	DXS9928E DNA segment on chromosome X (unique) 9928 expressed sequence	Nucleus. Has many charged residues and a possible nuclear localization signal	0.02
X02761	Hs.287820:73,Hs.321592:1	FN1 fibronectin 1	Cell adhesion, cell motility, cell adhesion, soluble fraction, signal transduction, extracellular matrix, extracellular space. Fibronectin 1; member of family of proteins found in plasma and extracellular matrix	0.02
AW968613	Hs.79428:166	BNIP3 BCL2/adenovirus E1B 19kD-interacting protein 3	Anti-apoptosis, apoptosis inhibitor. Bcl2-related protein 3; binds antiapoptotic viral E1B 19 kDa protein and cellular Bcl2 protein	0.02
AW972565	Hs.32399:24	ESTs, Weakly similar to S51797 vasodilator-stimulated phosphoprotein [H.sapiens]	Function unknown	0.02
AF045229	Hs.82280:81	RGS10 regulator of G-protein signalling 10	Regulator of G protein signaling (RGS) family members are regulatory molecules that act as GTPase activating proteins (GAPs) for G alpha subunits of heterotrimeric G proteins. RGS proteins are able to deactivate G protein subunits of the Gi alpha, Go alpha and Gq alpha subtypes. They drive G proteins into their inactive GDP-bound forms.	0.02
AW953853	Hs.292833:19	PAEP progestagen-associated endometrial protein (placental protein 14, pregnancy-associated endometrial alpha-2-globulin, alpha uterine protein)	Developmental processes. Placental protein 14 (Glycodelin); member of lipocalin superfamily, highly similar to beta-lactoglobulins	0.02
U52426	Hs.74597:75,Hs.157615:3	STIM1 stromal interaction molecule 1	Integral plasma membrane protein, positive control of cell proliferation. Very strongly similar to murine Stim1; are a transmembrane stromal cell protein	0.02
F06700	Hs.7879:115	IFRD1 interferon-related developmental regulator 1	Myoblast determination. Strongly similar to rat interferon-related developmental regulator 1; may play a role in muscle differentiation	0.02
AI798863	Hs.87191:8	ESTs	Function unknown	0.03
NA		C4001170:gi|6863176|gb|AAF30402.1|AF109924_1 (AF109924) sulfatase 1 precursor [Helix poma		0.03
H52761	Hs.141475:24	Homo sapiens cDNA clone IMAGE:178663	Function unknown	0.03

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
BE546947	Hs.44276:43	HOXC10 homeo box C10	Embryogenesis and morphogenesis, positive control of cell proliferation, RNA polymerase II transcription factor. Homeobox C10, member of the homeobox developmental regulator family; binds with HOXA13 and HOXC13 to the Lamin B2 origin; ortholog of Drosophila Abdominal-B	0.03
AU076643	Hs.313:257,Hs.32991 0:1	SPP1. secreted phosphoprotein 1 (osteopontin, bone sialoprotein I, early T-lymphocyte activation 1)	Ossification, extracellular matrix, skeletal development. Osteopontin (bone sialoprotein); bone and blood vessel extracellular matrix protein involved in calcification and atherosclerosis	0.03
#(NOCAT)		NM_015902*:Homo sapiens progestin induced protein (DD5), mRNA. VERSION NM_020967.1 GI		0.03
U20536	Hs.3280:20	CASP6 caspase 6, apoptosis-related cysteine protease	Induction of apoptosis, cysteine-type peptidase, proteolysis and peptidolysis. Caspase 6; a cysteine (thiol) protease; related to the ICE-subfamily of caspases	0.03
AA581602	Hs.41840:7	ESTs	Function unknown	0.03
AJ245210		gb:Homo sapiens mRNA for immunoglobulin gamma heavy chain variable region, partial, clone 1A-4G21.	Function unknown	0.03
X65965		H.sapiens SOD-2 gene for manganese superoxide dismutase		0.03
AI808770	Hs.30258:9	ESTs	Function unknown	0.03
BE386490	Hs.279663:51	PIR Pirin	Nucleus, transcription co-factor, transcription from Pol II promoter. Putative cofactor of the NFI/CTF1 transcriptional activator	0.03
AW581992	Hs.301434:104,Hs.32 9017:1	KIAA1387 KIAA1387 protein	Function unknown	0.03
U77534		Human clone 1A11 immunoglobulin variable region (VH5-D-JH4) gene, partial cds	Function unknown	0.03
AL034417	Hs.11169:194,Hs.109 58:1,Hs.74137:1	Gene 33/Mig-6	Function unknown	0.03
L10343	Hs.112341:96,Hs.196 8:1	Homo sapiens elafin precursor, gene, complete cds	Function unknown	0.03
AW518944	Hs.76325:80,Hs.2312 99:1	IGJ immunoglobulin J polypeptide, linker protein for immunoglobulin alpha and mu polypeptides	Linker protein for immunoglobulin alpha and mu polypeptides	0.03

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
W28729	Hs.236510:6	Human retina cDNA randomly primed sublibrary Homo sapiens cDNA, mRNA sequence	Function unknown	0.03
AI640160	Hs.74131:4	ARSE arylsulfatase E (chondrodysplasia punctata 1)	Arylsulfatase, skeletal development. Arylsulfatase E; likely involved in warfarin embryopathy.	0.03
U11862	Hs.75741:62	ABP1 amiloride binding protein 1 (amine oxidase (copper-containing))	Metabolism, peroxisome, amine oxidase, drug binding. Diamine oxidase (D-amino-acid oxidase histaminase, amiloride-binding protein); deaminates putrescine and histamine	0.03
AW295980	Hs.252741:3	ESTs	Function unknown	0.03
X59135	Hs.158110:4	H.sapiens mRNA for immunoglobulin 0-81VL		0.03
BE466173	Hs.379794	Homo sapiens mRNA; cDNA DKFZp686N0118 (from clone DKFZp686N0118)	Function unknown	0.03
#(NOCAT)		Target Exon		0.03
AI354722	Hs.127216:24	hypothetical protein FLJ13465	Function unknown	0.04
M90464	Hs.169825:45,Hs.408:1	Human collagen type IV alpha 5 chain (COL4A5) gene, 5' end	Function unknown	0.04
AA829286	Hs.332053:48,Hs.336462:10	SAA1 serum amyloid A1	Inflammatory response, high-density lipoprotein. Member of the serum amyloid A protein family; member of high density apolipoproteins.	0.04
AI333771	Hs.82204:8,Hs.228363:1	ESTs	Function unknown	0.04
BE465867; NM_014992	Hs.197751:66	DAAM1 dishevelled associated activator of morphogenesis 1	The protein encoded by this gene contains FH domains and belongs to a novel FH protein subfamily implicated in cell polarity, thought to function as a scaffolding protein.	0.04
BE616902	Hs.285313:145,Hs.4055:43	COPEB core promoter element binding protein	A trancriptional activator, capable of activating transcription approximately 4-fold either on homologous or heterologous promoters. The DNA binding and transcriptional activity of this protein, in conjunction with its expression pattern, suggests that this protein may participate in the regulation and/or maintenance of the basal expression of pregnancy-specific glycoprotein gene and possibly other TATA box-less genes.	0.04

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
AA430373		gb:zw20f11.s1 Soares ovary tumor NbHOT Homo sapiens cDNA clone IMAGE:769869 3' similar to gb:M63438 IG KAPPA CHAIN PRECURSOR V-III REGION (HUMAN);, mRNA sequence.	Function unknown	0.04
R27430	Hs.271565:3	ESTs	Function unknown	0.04
BE387335	Hs.283713:68	CTHRC1 collagen triple helix repeat containing 1	Function unknown	0.04
AW264102	Hs.39168:16	ESTs	Function unknown	0.04
NA		Target Exon	Function unknown	0.04
AW952323	Hs.129908:39	KIAA0591 protein	Function unknown	0.04
AA088177	Hs.172870:13	ESTs	Function unknown	0.04
BE614567	Hs.19574:123	MGC5469 hypothetical protein MGC5469	Function unknown	0.04
AL079658	Hs.338207:139,Hs.146559:1	FRAP1 FK506 binding protein 12-rapamycin associated protein 1	DNA repair, DNA recombination, cell cycle control, 1-phosphatidylinositol 3-kinase, inositol/phosphatidylinositol kinase. FKBP-rapamycin associated protein; phosphatidylinositol kinase that may mediate rapamycin inhibition of the cell cycle progression through G1	0.04
NM_002776	Hs.69423:46,Hs.275464:1	KLK10 kallikrein 10 (KLK10) (PRSSL1) (nes1)	Extracellular, serine-type peptidase. *Putative serine protease*	0.04
BE261944	Hs.118625:62	CYB561 cytochrome b-561	Energy pathways, secretory vesicle, cytochrome b5 reductase, secretory vesicle membrane, integral plasma membrane protein. Cytochrome b561; serves as a biological marker for adrenergic secretory vesicles	0.04
NM_006379	Hs.171921:50	SEMA3C sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3C	Drug resistance, immune response, cell growth and maintenance. Semaphorin E; member of a protein family involved in neuronal growth cone guidance	0.04
AI002238	Hs.11482:19	SFRS11 splicing factor, arginine/serine-rich 11	Nucleus, mRNA splicing, mRNA processing, pre-mRNA splicing factor, May have a role in pre-mRNA splicing; contains arginine/serine-rich domain and an RRM domain	0.04
#(NOCAT)		ENSP00000231844*:Ecotropic virus integration 1 site protein.		0.04
X81789	Hs.77897:149	SF3A3 splicing factor 3a, subunit 3, 60kD	Nucleus, spliceosome, mRNA splicing, mRNA processing, pre-mRNA splicing factor. Spliceosome-associated protein 3a, subunit 3; component of the essential heterotrimeric splicing factor SF3a; *contains a zinc finger*	0.04

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
NM_002122	Hs.198253:21	HLA-DQA1 major histocompatibility complex, class II, DQ alpha 1	Pathogenesis, class II major histocompatibility complex antigen. Alpha 1 chain of HLA-DQ1 class II molecule (Ia antigen); complex binds peptides and presents them to CD4+ T lymphocytes|Proteome	0.00
AB001914		Homo sapiens PACE4 gene, exon 23-25, complete cds	Function unknown	0.04
AA311919	Hs.69851:24	NOLA1 nucleolar protein family A, member 1 (H/ACA small nucleolar RNPs)	Involved in various aspects of rRNA processing and modification. Localize to the dense fibrillar components of nucleoli and to coiled (Cajal) bodies in the nucleus.	0.04
AI381750	Hs.283437:122,Hs.10065:58	HTGN29 protein	Function unknown	0.04
#(NOCAT)		NM_000636*:Homo sapiens superoxide dismutase 2, mitochondrial (SOD2), mRNA. expression) (RFX2), mRNA.	Mitochondrion, oxidative stress response, manganese superoxide dismutase. Manganese superoxide dismutase; intramitochondrial free radical scavenging enzyme; has strong similarity to murine Sod2.	0.04
AA292998	Hs.163900:25	ESTs	Function unknown	0.04
BE439580	Hs.75498:40	SCYA20 small inducible cytokine subfamily A (Cys-Cys), member 20	Chemokine, chemotaxis, immune response, signal transduction, extracellular space, cell-cell signalling, inflammatory response, antimicrobial humoral response. Cytokine A20 (exodus); chemotactic factor for lymphocytes, but not a chemotactic factor for monocytes	0.04
AI677897	Hs.76640:124	RGC32 RGC32 protein	Cytoplasm, cell cycle regulator, regulation of CDK activity. Strongly similar to RGC-32.	0.04
#(NOCAT)		Target Exon	Function unknown	0.04
N72403		Homo sapiens cDNA clone IMAGE:245132	Function unknown	0.05
BE003054	Hs.1695:46	MMP12 matrix metalloproteinase 12 (macrophage elastase)	Zinc binding, cell motility, macrophage elastase, extracellular matrix, proteolysis and peptidolysis. Matrix metalloprotease; degrades elastin	0.05
AL035588	Hs.153203:26,Hs.23391:1	Human DNA sequence from clone 696P19 on chromosome 6p12.3-21.2. Contains the gene for TFEB, an NPM1 (Nucleophosmin, Numatrin) pseudogene and the MDFI gene for MyoD family inhibitor (myogenic repressor I-MF). Contains ESTs, STSs, GSSs and two putative CpG islands, complete sequence	Function unknown	0.05
AI080491	Hs.93270:3	ESTs, Moderately similar to S65657 alpha-1C-adrenergic receptor splice form 2 [H.sapiens]	Function unknown	0.05

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
AW770994	Hs.30340:125	hypothetical protein KIAA1165	Function unknown	0.05
H24177	Hs.75262:69,Hs.238912:1	CTSO cathepsin O	Cysteine-type endopeptidase, proteolysis and peptidolysis. Cathepsin O; cysteine (thiol) protease	0.05
AF146761	Hs.20450:29	BCM-like membrane protein precursor	Function unknown	0.05
NM_001955	Hs.2271:45,Hs.306:1	EDN1 endothelin 1	Circulation, peptide hormone, soluble fraction, signal transduction, extracellular space, cell-cell signalling, blood pressure regulation, positive control of cell proliferation. Preproendothelin 1; precursor of the hormone endothelin 1	0.05
AI680737	Hs.289068:204,Hs.326198:1	TCF4 transcription factor 4	Nucleus, RNA polymerase II transcription factor, transcription regulation from Pol II promoter. Transcriptional activator; interacts with ITF1 (TCF3); contains basic helix-loop-helix domain|Proteome	0.05
AI752666	Hs.76669:183	NNMT nicotinamide N-methyltransferase	*Nicotinamide N-methyltransferase*; catalyzes the N-methylation of nicotinamide and other pyridines, structurally-related drugs and xenobiotics|Proteome	0.05
AA505445	Hs.300697:21	IGHG3 immunoglobulin heavy constant gamma 3 (G3m marker)	Constant region of heavy chain of IgG3	0.05
BE246649; NM_003955	Hs.345728	SOCS3 STAT induced STAT-inhibitor 3; suppressor of cytokine signalling 3	suppression of IL-6 mediated signalling	0.02
M86849	Hs.323733:62,Hs.300816:5	GJB2 gap junction protein, beta 2, 26kD (connexin 26)	Hearing, connexon, plasma membrane, connexon channel, cell-cell signalling, small molecule transport. Connexin 26; gap junction protein expressed in various tissues including cochlea.	0.00
AW963419	Hs.155223:20	STC2 stanniocalcin 2	Peptide hormone, cell-cell signalling, glycopeptide hormone, nutritional response pathway, cell surface receptor linked signal transduction. Stanniocalcin 2; may regulate metal ion homeostasis and inhibits phosphate uptake.	0.00
BE298665	Hs.14846:132	Homo sapiens mRNA; cDNA DKFZp564D016 (from clone	Function unknown	0.00
AK000637	Hs.46624:11	HSPC043 HSPC043 protein	Function unknown	0.00
BE077546	Hs.31447:27	ESTs, Moderately similar to A46010 X-linked retinopathy protein [H.sapiens]	Function unknown	0.00
T97307		gb:ye53h05.s1 Soares fetal liver spleen 1NFLS Homo sapiens cDNA clone IMAGE:121497 3',	Function unknown	0.00

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
		mRNA sequence.		
R24601	Hs.108300:46	Homo sapiens adenylosuccinate synthetase isozyme (ADSS) mRNA, complete cds	Function unknown	0.00
BE090176	Hs.179902:95	Interim-CDw92 antigen	choline transporter-like protein	0.00
AA393907	Hs.97179:22	ESTs	Function unknown	0.00
W28729	Hs.236510:6	Homo sapiens mRNA; cDNA DKFZp666D074 (from clone DKFZp666D074)	Function unknown	0.00
BE313754	Hs.13350:52	Homo sapiens mRNA; cDNA DKFZp586D0918	Function unknown	0.01
AW673081	Hs.54828:9	ESTs	Function unknown	0.01
AA356694	Hs.94011:42,Hs.7744:2,Hs.231043:1	HCA4 Hepatocellular carcinoma-associated protein HCA4	Function unknown	0.01
L08239	Hs.5326:11	MG61 Porcupine	amino acid system N transporter 2;	0.01
BE397649	Hs.94109:40	Homo sapiens cDNA FLJ34399 fis, clone HCHON2001359	Function unknown	0.01
NM_012317	Hs.45231:36	LDOC1 Leucine zipper, down-regulated in cancer 1	Nucleus, negative control of cell proliferation. Nuclear protein; contains a leucine zipper-like motif	0.01
NM_000947	Hs.74519:20	PRIM2A primase, polypeptide 2A (58kD)	DNA primase, DNA replication, priming, alpha DNA polymerase:primase complex. Subunit of DNA primase polypeptide 2A; part of the DNA polymerase alpha-primase complex	0.01
AJ250562	Hs.82749:133	Homo sapiens partial TM4SF2 gene for tetraspanin protein, exon 1 and joined CDS	Function unknown	0.01
AL040183	Hs.123484:24,Hs.326906:1	Homo sapiens mRNA; cDNA DKFZp686E1934 (from clone DKFZp686E1934)	Function unknown	0.01
BE207573	Hs.83321:32	NMB neuromedin B	Peptide hormone, soluble fraction, signal transduction, cell-cell signalling. Precursor of neuromedin B, a C-terminally amidated peptide hormone; similar to bombesin	0.01
BE564162	Hs.250820:45	FLJ14827 hypothetical protein FLJ14827	Function unknown	0.01

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
BE439580	Hs.75498:40	SCYA20 Small inducible cytokine subfamily A (Cys-Cys), member 20	Chemokine, chemotaxis, immune response, signal transduction, extracellular space, cell-cell signalling, inflammatory response, antimicrobial humoral response. Cytokine A20 (exodus); chemotactic factor for lymphocytes, but not a chemotactic factor for monocytes	0.01
AW067800	Hs.155223:52	STC2 stanniocalcin 2	Peptide hormone, cell-cell signalling, glycopeptide hormone, nutritional response pathway, cell surface receptor linked signal transduction. Stanniocalcin 2; may regulate metal ion homeostasis and inhibits phosphate uptake.	0.01
AA569756	Hs.87803:10	Homo sapiens cDNA FLJ30156 fis, clone BRACE2000487	Function unknown	0.01
AW138190	Hs.180248:8	ZNF124 zinc finger protein 124 (HZF-16)	DNA binding. C2H2 zinc-finger protein 124	0.01
AF126245	Hs.14791:48	ACAD8 acyl-Coenzyme A dehydrogenase family, member 8	Lipid metabolism, acyl-CoA dehydrogenase. Member of the acyl-Coenzyme A dehydrogenase family; alpha,beta-dehydrogenates acyl-CoA esters	0.01
L10343	Hs.112341:96,Hs.1968:1	Homo sapiens elafin precursor, gene, complete cds	elastase-specific inhibitor in bronchial secretions	0.01
NM_002514	Hs.235935:38	NOV nephroblastoma overexpressed gene	Insulin-like growth factor receptor binding protein. Insulin-like growth factor binding protein; may play a role in nephrogenesis	0.01
AI863735	Hs.186755:3	ESTs	Function unknown	0.01
NM_005397	Hs.16426:160,Hs.248780:1	PODXL podocalyxin-like	Integral plasma membrane protein. Transmembrane protein similar to rodent podocalyxins	0.01
W26391	Hs.301206:100	KIF3B kinesin family member 3B	Plus-end kinesin, microtubule motor, anterograde axon cargo transport, plus-end-directed kinesin ATPase, determination of left-right asymmetry. Similar to murine Kif3b; may have a role in intracellular organelle transport, may act in left-right determination in embryogenesis; are a microtubule-associated motor protein	0.01
H15474	Hs.132898:156	FADS1 fatty acid desaturase 1	C-5 sterol desaturase, fatty acid desaturation, integral membrane protein. Delta-5 desaturase; catalyzes production of polyenoic fatty acids such as arachidonic acid	0.01
U51166	Hs.173824:106	TDG Thymine-DNA glycosylase	DNA repair, nucleoplasm, damaged DNA binding, base-excision repair, G/T-mismatch-specific thymine-DNA glycosylase. Thymine-DNA glycosylase; excises uracil and thymine from mispairs with guanidine	0.01
AA243499	Hs.104800:23	FLJ10134 hypothetical protein FLJ10134	Highly similar to murine p19.5; are a membrane protein	0.01
AW408807	Hs.34497:46	FLJ22116 hypothetical protein FLJ22116	Function unknown	0.01

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
AI738719	Hs.198427:98	HK2 *Hexokinase 2*	Hexokinase, cell cycle control, glucose catabolism, glucose metabolism, mitochondrial outer membrane. Hexokinase II; converts aldo- and keto-hexose sugars to the hexose-6-phosphate	0.01
AB040888	Hs.41793:110	*Homo sapiens* mRNA for KIAA1455 protein, partial cds	Function unknown	0.01
BE313077	Hs.93135:40,Hs.228357:1	Homo sapiens cDNA FLJ39971 fis, clone SPLEN2028066	Function unknown	0.01
AI677897	Hs.76640:124	RGC32 RGC32 protein	Cytoplasm, cell cycle regulator, regulation of CDK activity. Strongly similar to RGC-32	0.01
C14898	Hs.192986:5	ESTs	Function unknown	0.01
AI821730	Hs.116524:7	Homo sapiens cDNA FLJ35800 fis, clone TESTI2005933	Function unknown	0.01
AF007393	Hs.177574:111	PRKRIR protein-kinase, interferon-inducible double stranded RNA dependent inhibitor, repressor of (P58 repressor)	Stress response, protein binding, signal transduction, translational regulation, negative control of cell proliferation. Regulates interferon-induced protein kinase PKR (PRKR) activity by binding and inhibiting the PKR-regulator P58IPK (PRKRI)	0.01
H65423	Hs.17631:42	DKFZP434E2135 hypothetical protein DKFZp434E2135	Function unknown	0.01
N46243	Hs.110373:26	ESTs, Highly similar to T42626 secreted leucine-rich repeat-containing protein SLIT2 - mouse (fragment) [M.musculus]	Function unknown	0.01
AA095971	Hs.198793:56,Hs.309674:7	Homo sapiens cDNA: FLJ22463 fis, clone HRC10126	Function unknown	0.01
U20350	Hs.78913:33	CX3CR1 chemokine (C-X3-C) receptor 1	Virulence, chemotaxis, coreceptor, cell adhesion, plasma membrane, chemokine receptor, response to wounding, cellular defense response, integral plasma membrane protein, G-protein linked receptor protein signalling pathway. CX3C chemokine receptor; G protein-coupled receptor, mediates leukocyte migration and adhesion, binds the CX3C chemokine fractalkine and signals through a pertussis toxin sensitive G-protein	0.01
NM_005756	Hs.184942:18	GPR64 G protein-coupled receptor 64	Spermatogenesis, G-protein linked receptor, integral plasma membrane protein, G-protein linked receptor protein signalling pathway. Member of the G protein-coupled receptor family	0.01
D19589	Hs.13453:87	FLJ14753 hypothetical protein FLJ14753	Function unknown	0.02
AW957446	Hs.301711:74	ESTs	Function unknown	0.02

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
AW294647	Hs.233634:40	C20orf39 chromosome 20 open reading frame 39	Function unknown	0.02
BE159718	Hs.85335:46	Homo sapiens, clone IMAGE:4513159, mRNA	Function unknown	0.02
AI888490	Hs.55902:22	EDG3 endothelial differentiation, sphingolipid G-protein-coupled receptor, 3	Lipid binding, plasma membrane, inflammatory response, G-protein linked receptor, embryogenesis and morphogenesis, integral plasma membrane protein, positive control of cell proliferation, cytostolic calcium ion concentration elevation, G-protein linked receptor protein signalling pathway. Lysosphingolipid receptor, a G protein-coupled receptor; activates calcium flux and serum response element driven transcription	0.02
AA022569	Hs.29802:35,Hs.271785:1	ESTs	Function unknown	0.02
BE147740	Hs.104558:21	ESTs, Moderately similar to hypothetical protein FLJ20378 [Homo sapiens]	Function unknown	0.02
AI798863	Hs.87191:8	ESTs	Function unknown	0.02
BE464341	Hs.21201:18	Interim-DKFZP566B0846: nectin 3	Low similarity to PVRL1; are a membrane glycoprotein; contains an immunoglobulin (Ig) domain	0.02
AL080235	Hs.35861:34,Hs.289068:1	RIS1 Ras-induced senescence 1	Rat brain specific binding protein	0.02
AI557212	Hs.17132:102,Hs.330782:1	ESTs	Function unknown	0.02
X75208	Hs.2913:41	EPHB3 EphB3	Signal transduction, integral plasma membrane protein, transmembrane receptor protein tyrosine kinase. Eph-related receptor tyrosine kinase B3	0.02
AA628980	Hs.192371:3	DSCR8 Down syndrome critical region protein DSCR8	Melanoma-testis-associated protein 2	0.02
BE242587	Hs.118651:39	HHEX hematopoietically expressed homeobox	Nucleus, DNA binding, transcription factor, developmental processes, antimicrobial humoral response. Member of the homeodomain family of DNA binding proteins; may regulate gene expression, morphogenesis, and differentiation	0.02
NM_005512	Hs.151641:65	GARP glycoprotein A repetitions predominant	Integral plasma membrane protein. Putative transmembrane cell surface protein; has an extracellular domain comprised largely of leucine-rich repeats	0.02
AW953853	Hs.292833:19	PAEP progestagen-associated endometrial protein (placental protein 14, pregnancy-associated endometrial alpha-2-globulin, alpha uterine	Developmental processes. Placental protein 14 (Glycodelin); member of lipocalin superfamily, highly similar to beta-lactoglobulins	0.02

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
		protein)		
AU076611	Hs.154672:122	MTHFD2 methylene tetrahydrofolate dehydrogenase (NAD dependent), methenyltetrahydrofolate cyclohydrolase	Mitochondrion, electron transporter, methenyltetrahydrofolate cyclohydrolase, methylenetetrahydrofolate dehydrogenase. NAD-dependent methylene tetrahydrofolate dehydrogenase-cyclohydrolase; may provide formyltetrahydrofolate for formylmethionyl tRNA synthesis; involved in initiation of mitochondrial protein synthesis	0.02
AW968613	Hs.79428:166	BNIP3 BCL2/adenovirus E1B 19kD-interacting protein 3	Anti-apoptosis, apoptosis inhibitor. Bcl2-related protein 3; binds antiapoptotic viral E1B 19 kDa protein and cellular Bcl2 protein	0.02
AL353944	Hs.50115:14	Homo sapiens mRNA; cDNA DKFZp761J1112 (from clone DKFZp761J1112)	Function unknown	0.02
BE614149	Hs.20814:29,Hs.306626:27	LOC51072: C21orf19-like protein	Function unknown	0.02
AA292998	Hs.163900:25	ESTs	Highly similar to winged helix/forkhead transcription factor	0.02
H12912	Hs.274691:138	AK3 adenylate kinase 3	Nucleobase, nucleoside, nucleotide and nucleic acid metabolism. Adenylate kinase 3; strongly similar to murine Ak4	0.02
AA188763	Hs.36793:4	SLC12A8 solute carrier family 12 (potassium/chloride transporters), member 8	Solute carrier family 12 (potassium/chloride transporters), member 8	0.02
AK000596	Hs.3618:56	HPCAL1 hippocalcin-like 1	Calcium-binding protein with similarity to hippocalin (human HPCA); expressed only in the brain.	0.02
AI970797	Hs.64859:16	ESTs	Function unknown	0.02
AW519204	Hs.40808:22	ESTs	Function unknown	0.02
Z42387	Hs.83883:114	TMEPAI transmembrane, prostate androgen induced RNA	Function unknown	0.02
AF145713	Hs.61490:51	SCHIP1 schwannomin-interacting protein 1	Cytoplasm. Associates with the neurofibromatosis type 2 protein schwannomin (NF2); contains a coiled-coil domain	0.02
AA972412	Hs.13755:41	FBXW2 f-box and WD-40 domain protein 2	Protein modification, ubiquitin--protein ligase, proteolysis and peptidolysis, ubiquitin conjugating enzyme. F-box and WD-40 domain protein 2; putative SCF ubiquitin ligase subunit involved in protein degradation; contains a WD-40 domain and an F-box	0.02
AK001564	Hs.104222:139,Hs.296267:4	Homo sapiens cDNA FLJ10702 fis, clone NT2RP3000759, weakly similar to ADP-RIBOSYLATION FACTOR	Member of the ADP-ribosylation factor (ARF) family; putative GTP-binding protein involved in protein trafficking	0.02

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
AW959861	Hs.290943:28	ESTs	Function unknown	0.02
BE313555	Hs.7252:158	RAI17 retinoic acid induced 17	Function unknown	0.02
W25005	Hs.24395:199	zb67e02.r1 Soares_fetal_lung_NbHL19W Homo sapiens cDNA clone IMAGE:308666 5', mRNA sequence	Function unknown	0.02
AI193356	Hs.160316:3	ESTs	Function unknown	0.02
AF111106	Hs.3382:223	PPP4R1 Protein phosphatase 4, regulatory subunit 1	Protein phosphatase	0.02
AI130740	Hs.6241:116	PIK3R1 phosphoinositide-3-kinase, regulatory subunit, polypeptide 1 (p85 alpha)	A family of enzymes that phosphorylate the 3'-hydroxyl of phosphatidylinositol (PtdIns).	0.02
AA985190	Hs.246875:42	FLJ20059 hypothetical protein FLJ20059	Contains four Kelch motif domains	0.02
BE221880	Hs.268555:144	XRN2 5'-3' exoribonuclease 2	Nucleus, nuclease, recombination, RNA catabolism, RNA processing. 5'-3' Exoribonuclease; similar to Schizosaccharomyces pombe Dhp1p	0.03
AF084545		Homo sapiens versican Vint isoform, mRNA, partial cds	Function unknown	0.03
R26584	Hs.267993:43	TAPBP-R: TAP binding protein related	Has low similarity to TAPBP (Tapasin); contains two immunoglobulin (Ig) domains|Proteome	0.03
AW247380	Hs.12124:116	ELAC2 elaC homolog 2 (E. coli)	putative prostate cancer susceptibility protein	0.03
AA364261	Hs.131365:7	ESTs	Weakly similar to T31613 hypothetical protein Y50E8A.l - Caenorhabditis elegans [C.elegans]	0.03
U25849	Hs.75393:141	ACP1 Human red cell-type low molecular weight acid phosphatase (ACP1) gene, exon 6 and 7, complete cds	Acid phosphatase	0.03
AF262992	Hs.123159:14	SPAG4 Sperm associated antigen 4	Spermatogenesis, structural protein. Sperm associated antigen 4; predicted ortholog of rat SPAG4, which interacts with rat ODF27, the 27kDa outer dense fiber protein of elongating spermatids	0.03
AW342140	Hs.182545:1	ESTs, Weakly similar to POL2_MOUSE Retrovirus-related POL polyprotein	Function unknown	0.03
AL133572	Hs.199009:58	PCCX2 protein containing CXXC domain 2	DNA-binding protein with PHD finger and CXXC domain, is regulated by proteolysis.	0.03

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
AI497778	Hs.20509:4	HBXAP Hepatitis B virus x associated protein	Weakly similar to Drosophila CG8677	0.03
AI745379	Hs.42911:31	TAF13 TAF13 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 18 kD	TFIID complex, protein binding, transcription factor, general RNA polymerase II transcription factor. TBP-associated factor K; component of TFIID complexes containing TAFII30 (TAF2H)	0.03
U51712	Hs.13775:135	LAGY: lung cancer-associated Y protein	The protein encoded by this gene is a lung cancer associated protein. The function of the protein is not known. Multiple alternatively spliced transcript variants have been described for this gene but some of their full length sequence has not been determined.	0.03
AW375974	Hs.156704:4	ESTs	Function unknown	0.03
AF251237	Hs.112208:16	GAGED2 G antigen, family D, 2	GAGE genes are expressed in a variety of tumors and in some fetal and reproductive tissues. This gene is strongly expressed in Ewing's sarcoma, alveolar rhabdomyosarcoma and normal testis. The protein encoded by this gene contains a nuclear localization signal and shares a sequence similarity with other GAGE/PAGE proteins. Because of the expression pattern and the sequence similarity, this protein also belongs to a family of CT (cancer-testis) antigens.	0.03
NM_000636		Homo sapiens superoxide dismutase 2, mitochondrial (SOD2), mRNA. expression) (RFX2), mRNA.	Mitochondrion, oxidative stress response, manganese superoxide dismutase. Manganese superoxide dismutase; intramitochondrial free radical scavenging enzyme; has strong similarity to murine Sod2.	0.02
AA130986	Hs.271627:1	ESTs	Function unknown	0.01
AA216363	Hs.262958:48,Hs.327737:2	DKFZP434B044 hypothetical protein DKFZp434B044	Function unknown	0.01
AA628980	Hs.192371:3	DSCR8 down syndrome critical region protein DSCR8	Function unknown	0.00
AA811657	Hs.220913:9	Homo sapiens cDNA FLJ40827 fis, clone TRACH2011500	Function unknown	0.02
AA897108		gb:am08a08.s1 Soares_NFL_T_GBC_S1 Homo sapiens cDNA clone 3', mRNA sequence	Function unknown	0.01
AB040888	Hs.41793:110	Homo sapiens mRNA for KIAA1455 protein, partial cds	Function unknown	0.02

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
AF212225	Hs.283693:104	Homo sapiens BM022 mRNA, complete cds	Function unknown	0.02
AI089575	Hs.9071:52	ESTs	Function unknown	0.02
AI282028	Hs.25205:10	ESTs	Function unknown	0.02
AI368826	Hs.30654:15	FLJ10849: hypothetical protein FLJ10849	Moderately similar to members of the septin family	0.02
AI718702	Hs.308026:11,Hs.194490:6	HLA-DRB3 major histocompatibility complex, class II, DR beta 5	Signal transduction, integral plasma membrane protein, class II major histocompatibility complex antigen. Beta 3 chain of HLA-DR; subunit of MHC class II molecule, complex binds peptides and presents them to CD4+ T lymphocytes	0.02
AI827248	Hs.224398:3	Homo sapiens cDNA FLJ11469 fis, clone HEMBA1001658	Function unknown	0.01
AK002039	Hs.26243:38	MRVI1 murine retrovirus integration site 1 homolog	Oncogenesis, tumor suppressor, endoplasmic reticulum membrane. Similar to human MLRP; may act as a tumor suppressor	0.02
AL109791	Hs.241559:3	Homo sapiens mRNA full length insert cDNA clone EUROIMAGE 151432	Function unknown	0.00
AW090198	Hs.4779:29	LOC127829: hypothetical protein BC015408	Function unknown	0.01
AW296454	Hs.24743:92	FLJ20171: hypothetical protein FLJ2017	Contains three RNA recognition motifs (RRM, RBD, or RNP)	0.02
AW445034	Hs.256578:4	ESTs	Function unknown	0.00
AW452948	Hs.257631:3	ESTs	Function unknown	0.01
AW470411	Hs.288433:27	HNT: neurotrimin	Cell adhesion, neuronal cell recognition, integral plasma membrane protein. Neurotrimin; may function as a GPI-anchored neural cell adhesion molecule; *member of the immunoglobulin superfamily*	0.02
AW885727	Hs.301570:22	FST follistatin	Developmental processes. Follistatin; inhibits the release of follicle-stimulating hormone (FSH)	0.01
AW970859	Hs.313503:4	ESTs	Function unknown	0.02
AW979189	Hs.283367:3	ESTs	Function unknown	0.01

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
BE165866	Hs.83623:66	Human XIST, coding sequence "a" mRNA (locus DXS399E)	XIST mRNA	0.01
BE175582		gb:RC5-HT0580-100500-022-C01 HT0580 Homo sapiens cDNA, mRNA sequence	Function unknown	0.01
BE242587	Hs.118651:39	HHEX hematopoietically expressed homeobox	Nucleus, DNA binding, transcription factor, developmental processes, antimicrobial humoral response. Member of the homeodomain family of DNA binding proteins; may regulate gene expression, morphogenesis, and differentiation|	0.01
BE271927	Hs.87385:31,Hs.307940:4	LOC115416: hypothetical protein BC012331	Function unknown	0.01
BE439580	Hs.75498:40	SCYA20 small inducible cytokine subfamily A (Cys-Cys), member 20	Chemokine, chemotaxis, immune response, signal transduction, extracellular space, cell-cell signalling, inflammatory response, antimicrobial humoral response. Cytokine A20 (exodus); chemotactic factor for lymphocytes, but not a chemotactic factor for monocytes	0.02
BE464016	Hs.238956:35	Homo sapiens cDNA FLJ37793 fis, clone BRHIP3000473	Function unknown	0.02
D63216	Hs.153684:137	FRZB frizzled-related protein	Membrane, extracellular, skeletal development. Frizzled-related protein; similar to frizzled family of receptors	0.02
F34856	Hs.292457:120	Homo sapiens, clone MGC:16362 IMAGE:3927795, mRNA, complete cds	Function unknown	0.02
M83822	Hs.62354:112	LRBA LPS-responsive vesicle trafficking, beach and anchor containing	May mediate protein-protein interactions; contains two WD domains (WD-40 repeats) and a beige/BEACH domain|Proteome	0.02
N33937	Hs.10336:6	ESTs	Function unknown	0.01
N49068	Hs.93966:4	ESTs	Function unknown	0.01
N51357	Hs.260855:62	NSE1: NSE1	Function unknown	0.02
N80486	Hs.39911:17	Homo sapiens mRNA for FLJ00089 protein, partial cds	Function unknown	0.02
NM_000954	Hs.8272:265,Hs.332355:1	PTGDS prostaglandin D2 synthase (21kD, brain)	Membrane, prostaglandin-D synthase. Glutathione-independent prostaglandin D2 synthase; membrane associated, catalyzes synthesis of prostaglandin D; member of the lipocalin family of transporters	0.02
NM_005756	Hs.184942:18	GPR64 G protein-coupled receptor 64	Spermatogenesis, G-protein linked receptor, integral plasma membrane protein, G-protein linked receptor protein signalling pathway. Member of the G protein-coupled receptor family	0.02

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
NM_016652	Hs.268281:61	CRNKL1 Crn, crooked neck-like 1 (Drosophila)	Function unknown	0.02
R26584	Hs.267993:43	TAPBP-R: TAP binding protein related	Has low similarity to TAPBP (Tapasin); contains two immunoglobulin (Ig) domains	0.01
R31178	Hs.287820:6	FN1 fibronectin 1	Cell adhesion, cell motility, cell adhesion, soluble fraction, signal transduction, extracellular matrix, extracellular space. Fibronectin 1; member of family of proteins found in plasma and extracellular matrix	0.02
W05391	Hs.83623:8	Homo sapiens cDNA FLJ30298 fis, clone BRACE2003172	Function unknown	0.02
W25005	Hs.24395:199	zb67e02.r1 Soares_fetal_lung_NbHL19W Homo sapiens cDNA clone IMAGE:308666 5', mRNA sequence	Function unknown	0.01
W45393	Hs.55888:15	ATF7 activating transcription factor 7	Transcription factor. Leucine zipper DNA-binding protein; recognizes a cAMP response element (CRE), involved in the regulation of adenovirus Ela-responsive and cellular cAMP-inducible promoters	0.02
W68815	Hs.301885:20	Homo sapiens cDNA FLJ33794 fis, clone CTONG1000009	Function unknown	0.01
X65965		H.sapiens SOD-2 gene for manganese superoxide dismutase	Mitochondrion, oxidative stress response, manganese superoxide dismutase. Manganese superoxide dismutase; intramitochondrial free radical scavenging enzyme; has strong similarity to murine Sod2.	0.01
X76732	Hs.3164:58	NUCB2 nucleobindin 2	Cytosol, DNA binding, plasma membrane, calcium binding, extracellular space. Nucleobindin 2; may bind DNA and calcium; has DNA-binding and EF-hand domains, and a leucine-zipper	0.02
Z45051	Hs.22920:25	C20orf103 chromosome 20 open reading frame 103	Low similarity to a region of murine Lamp1|Proteome	0.02

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
c. downregulated genes				
NM_022117	Hs.136164:23	SE20-4, cutaneous T-cell lymphoma-associated tumor antigen se20-4se20-4	Cutaneous T-cell lymphoma-associated tumor antigen se20-4se20-4; differentially expressed nucleolar TGF-beta1 target protein (DENTT); also known as CDA1	0
NM_005460	Hs.24948:32, Hs.300445:4	SNCAIP, synuclein, alpha interacting protein (synphilin)	Cytoplasm, pathogenesis, protein binding. Synphilin-1; promotes formation of cytosolic inclusions in neurons (SNCAIP). Synuclein alpha interacting protein contains several protein-protein interaction domains and interacts with alpha synuclein in neurons. Mutations of SNCAIP have been linked to Parkinson disease.	0
NM_002387	Hs.1345:5	MCC, mutated in colorectal cancers	Receptor, signal transduction, tumor suppressor. Similar to the G protein-coupled m3 muscarinic acetylcholine receptor. MCC is a candidate for the putative colorectal tumor suppressor gene. The MCC gene product are involved in early stages of colorectal neoplasia in both sporadic and familial tumors.	0
AI745249	Hs.23650:30	Homo sapiens, clone MGC:9889 IMAGE:3868330	Function unknown	0.0009
AI694200	Hs.356620, Hs.227913:11	ESTs	Function unknown	0.0442

Table 2
Genes having modified expression in serous ovarian cancer relative to normal ovarian tissue

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	Ratio
M25809	Hs.64173	ATP6V1B1, ATPase, H+ transporting, lysosomal 56/58kD, V1 subunit B, isoform 1 (Renal tubular acidosis with deafness)	Subunit B1 (beta subunit) of a vacuolar-type H+-ATPase 1; apical proton pump that mediates distal nephron acid secretion	1062.30
AW959311	Hs.172012	DKFZP434J037: hypothetical protein DKFZp434J037	Function unknown	227.83
H16423	Hs.82685	Homo sapiens mRNA; cDNA DKFZp313F0317 (from clone DKFZp313F0317)	Function unknown	74.54
AI733848	Hs.71935	ZNF339, zinc finger protein 339	Zinc finger protein	55.13
AW055308	Hs.31803	NAC1, transcriptional repressor NAC1	Function unknown	52.63
AF034102	Hs.32951	SLC29A2, solute carrier family 29 (nucleoside transporters), member 2	Nitrobenzylthioinosine-insensitive equilibrative nucleoside transporter 2; may act in the uptake of purine and pyrimidine nucleosides	44.34
AI791905	Hs.95549	FLJ20273: RNA-binding protein	Contains four RNA recognition motifs (RRM, RBD, or RNP)	43.21
AW296454	Hs.24743	FLJ20171: hypothetical protein FLJ20171	Contains three RNA recognition motifs (RRM, RBD, or RNP)	38.91
Z43989	Hs.82141	Human clone 23612 mRNA sequence	Function unknown	37.89
AL043980	Hs.7886	PELI1, pellino homolog 1 (Drosophila)	Pellino protein	35.20
BE514982	Hs.38991	S100A2, S100 calcium binding protein A2	S100 calcium-binding protein A2; interacts with target proteins to link extracellular stimuli and cellular responses; member of the S100 tissue/cell specific Ca2+-binding protein family	34.53
		Target Exon	Function unknown	34.02
AI811807	Hs.108646	Homo sapiens cDNA FLJ12534 fis, clone NT2RM4000244	Function unknown	32.34
U90441	Hs.3622	P4HA2, procollagen-proline, 2-oxoglutarate 4-dioxygenase (proline 4-hydroxylase), alpha polypeptide II	Alpha 2 subunit of prolyl 4-hydroxylase; catalyzes the formation of 4-hydroxyproline in collagens	32.24
T98226	Hs.171952	OCLN, occludin	This gene encodes an integral membrane protein which is located at tight junctions. This protein are involved in the formation and maintenance of the tight junction.	31.56

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	Ratio
R35343	Hs.24988	Human DNA sequence from clone RP1-233G16 on chromosome Xq22.1-23. Contains the 5' part of a novel gene, ESTs, STSs, GSSs and a putative CpG island		31.22
BE247295	Hs.78452	SLC20A1, solute carrier family 20 (phosphate transporter), member 1	Sodium-dependent phosphate symporter; acts as a cell-surface receptor for gibbon ape leukemia virus	30.16
AB037734	Hs.4993	PCDH19, protocadherin	Protocadherin	29.90
		C5000394*:gi|12737280|ref|XP_006682.2| keratin 18 [Homo sapiens]||6633	Function unknown	29.30
AF212223	Hs.25010	Homo sapiens BM025 mRNA, complete cds	Function unknown	28.85
AA902656	Hs.21943	NIF3L1, NIF3 (Ngg1 interacting factor 3, S.pombe homolog)-like 1	Amyotrophic lateral sclerosis 2 (juvenile) chromosome region, candidate 1	27.73
X14008	Hs.234734	Human lysozyme gene (EC 3.2.1.17)	Lysozyme	27.66
AA570256		LOC116238: hypothetical protein BC014072	Function unknown	27.52
AA137152	Hs.286049	PSA, phosphoserine aminotransferase	The protein encoded by this gene is likely a phosphoserine aminotransferase, based on similarity to proteins in mouse, rabbit, and Drosophila. Alternative splicing of this gene results in two transcript variants encoding different isoforms.	25.57
BE621807		TM4SF1, transmembrane 4 superfamily member 1	L6 antigen; member of the transmembrane 4 superfamily (TM4SF)	25.40
AB041036	Hs.57771	KLK11, kallikrein 11	Trypsin-like serine protease; has serine protease activity	25.05
F13386	Hs.7888	Homo sapiens clone 23736 mRNA sequence	Function unknown	22.50
AA158177	Hs.118722	FUT8, fucosyltransferase 8 (alpha (1,6) fucosyltransferase)	N-linked glycosylation, oligosaccharide biosynthesis, glycoprotein 6-alpha-L-fucosyltransferase. Alpha(1,6)fucosyltransferase (GDP-L-Fuc:N-acetyl-beta-D-glucosaminide:alpha1-6 fucosyltransferase); transfers fucose to N-linked type complex glycopeptides from GDP-Fuc; functions in asparagine-linked glycoprotein oligosaccharide synthesis	21.90
BE267045	Hs.75064	TBCC, tubulin-specific chaperone c	Tubulin-specific chaperone c; cofactor in the folding pathway of beta-tubulin, mediates the release of beta-tubulin polypeptides committed to the native state	21.49
		NM_005936:Homo sapiens myeloid/lymphoid or mixed-lineage leukemia (trithorax (Drosophila) homolog); translocated to, 4 (MLLT4), mRNA.	Function unknown	20.46

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	Ratio
AA150864	Hs.790	MGST1, microsomal glutathione S-transferase 1	Microsome, glutathione transferase. Microsomal glutathione S-transferase; catalyzes the conjugation of glutathione to electrophilic compounds; member of a family of detoxication enzymes.	20.35
AW955632	Hs.66666	EST367702 MAGE resequences, MAGD Homo sapiens cDNA, mRNA sequence	Function unknown	20.26
AW837046	Hs.6527	QV1-LT0037-150200-069-e09 LT0037 Homo sapiens cDNA, mRNA sequence	Function unknown	19.60
AA286887	Hs.24724	MFHAS1, malignant fibrous histiocytoma amplified sequence 1	The primary structure of its product includes an ATP/GTP-binding site, three leucine zipper domains, and a leucine-rich tandem repeat, which are structural or functional elements for interactions among proteins related to the cell cycle, and which suggest that overexpression might be oncogenic with respect to MFH.	19.16
AW401864	Hs.18720	PDCD8: programmed cell death 8 (apoptosis-inducing factor)	Mitochondrial apoptosis-inducing factor; flavoprotein inducing chromatin condensation and DNA fragmentation	19.01
AA196241	Hs.73980	zp98f03.r1 Stratagene muscle 937209 Homo sapiens cDNA clone IMAGE:628253 5' similar to gb:M19309 TROPONIN T, SLOW SKELETAL MUSCLE ISOFORMS (HUMAN);, mRNA sequence	Function unknown	18.82
NM_004998	Hs.82251	MYO1E, myosin IE	Highly similar to class I myosin; may bind proline-rich peptides; contains an Src homology 3 (SH3) and myosin head domain (motor domain)	18.62
AW873704	Hs.320831	C20orf72: chromosome 20 open reading frame 72	Function unknown	18.19
AW361666	Hs.49500	KIAA0746: KIAA0746 protein	Function unknown	18.05
BE174595	Hs.366	PTS, 6-pyruvoyltetrahydropterin synthase	6-Pyruvoyltetrahydropterin synthase; synthesizes tetrahydrobiopterin, activity requires sepiapterin reductase, Mg2+, and NADPH	17.28
M31669	Hs.1735	Human inhibin beta-B-subunit gene, exon 2, and complete cds	Function unknown	16.24
AK001714	Hs.95744	FLJ10852, hypothetical protein similar to ankyrin repeat-containing priotein AKR1	Are involved in protein-protein interactions; has five ankyrin repeats and a DHHC-type zinc finger or NEW1 domain	16.09
AU076517	Hs.184276	AU076517 Sugano cDNA library Homo sapiens cDNA clone ColF3385 similar to 5'-end region of Homo sapiens ezrin-radixin-moesin binding phosphoprotein-50 mRNA, mRNA sequence	Function unknown	16.05

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	Ratio
NM_006456	Hs.288215	STHM, sialyltransferase	Low similarity to beta-galactosidase a-2,3-sialytransferase SIAT4B; member of the sialyltransferase family	15.93
BE148235	Hs.193063	Homo sapiens cDNA FLJ14201 fis, clone NT2RP3002955	Function unknown	15.91
AV653729	Hs.8185	SQRDL: sulfide dehydrogenase like (yeast)	Sulfide dehydrogenase like	15.35
AL119671	Hs.1420	FGFR3, fibroblast growth factor receptor 3 (achondroplasia, thanatophoric dwarfism)	Fibroblast growth factor receptor 3; receptor tyrosine kinase that binds acidic and basic FGF	14.62
AA393071	Hs.182579	LAP3, leucine aminopeptidase	Leucine aminopeptidase	14.60
AL048753	Hs.303649	CCL2, chemokine (C-C motif) ligand 2	Cytokine A 2; chemotactic factor for monocytes	14.37
AI868872	Hs.282804	CP, ceruloplasmin (ferroxidase)	Ceruloplasmin; ferrous oxidase, binds copper in plasma and maintains iron homeostasis	14.07
NM_004419	Hs.2128	DUSP5, dual specificity phosphatase 5	Mitogen inducible dual specificity protein phosphatase 5; dephosphorylates extracellular signal-regulated kinase	14.05
AW969587	Hs.86366	EST381664 MAGE resequences, MAGK Homo sapiens cDNA, mRNA sequence	Function unknown	13.75
AW161449	Hs.72290	WNT7A, wingless-type MMTV integration site family, member 7A	Very strongly similar to murine Wnt7a; may have a role in limb development and sexual dimorphism; member of the Wnt family of cell signalling proteins	13.48
BE409838	Hs.194657	CDH1, cadherin 1, type 1, E-cadherin (epithelial)	E-cadherin (uvomorulin); Ca2+-dependent glycoprotein, mediates cell-cell interactions in epithelial cells	12.92
BE540274	Hs.239	FOXM1, forkhead box M1	Cell-cycle regulated HNF-3/fork head; a transcriptional regulator	12.86
AF022375	Hs.73793	VEGF, vascular endothelial growth factor	Vascular endothelial growth factor; induces endothelial cell proliferation and vascular permeability	12.79
AW369278	Hs.23412	FLJ20160: hypothetical protein FLJ20160	Function unknown	12.73
AF147204	Hs.89414	CXCR4, chemokine (C-X-C motif), receptor 4 (fusin)	CXC chemokine receptor (fusin); G protein-coupled receptor binds CXC cytokines, mediates intracellular calcium flux	12.56
BE242818	Hs.311609	DDX39, DEAD/H (Asp-Glu-Ala-Asp/His) box polypeptide 39	Strongly similar to human D6S81E; member of the DEAD/H box ATP-dependent RNA helicase family	12.43
NM_014791	Hs.184339	MELK, maternal embryonic leucine zipper kinase	Leucine zipper kinase	12.25
U38847	Hs.151518	TARBP1, TAR (HIV) RNA binding protein 1	Binds to the HIV-1 TAR RNA regulatory element, may function alone or with HIV-1 Tat to disengage RNA polymerase II during transcriptional elongation; has a leucine zipper	12.22
AW953575	Hs.303125	EST365645 MAGE resequences, MAGC Homo sapiens cDNA, mRNA sequence	Function unknown	12.21

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	Ratio
AI949095	Hs.67776	ESTs, Weakly similar to T22341 hypothetical protein F47B8.5 - Caenorhabditis elegans [C.elegans]	Homo sapiens, clone IMAGE:5455669, mRNA, partial cds	12.08
BE274530	Hs.273333	FLJ10986, hypothetical protein FLJ10986	Member of the FGGY carbohydrate kinase family	11.75
AB020676	Hs.21543	KIAA0869 protein	Function unknown	11.73
		Target Exon	Function unknown	11.69
H48299	Hs.26126:33	CLDN10, claudin 10	Cell adhesion, integral plasma membrane protein, tight junction.	11.67
T34530	Hs.4210	Homo sapiens cDNA FLJ13069 fis, clone NT2RP3001752	Function unknown	11.50
NM_022454	Hs.97984	SOX17, SRY (sex determining region Y)-box 17	SRY-related HMG-box transcription factor SOX17	11.42
AA737033	Hs.7165	Homo sapiens, clone IMAGE:4428577, mRNA, partial cds	Function unknown	10.79
AA433988	Hs.98502:8	MUC16, mucin 16, CA125	Mucin 16. Alias CA125 ovarian cancer antigen	10.52
H91282	Hs.286232	Homo sapiens cDNA: FLJ23190 fis, clone LNG12190	Function unknown	10.50
AW005054	Hs.47883	LOC57118: CamKI-like protein kinase	CamKI-like protein kinase; granulocyte-specific protein kinase that activates ERK/MAP kinase activity; similar to Ca(2+)-calmodulin-dependent kinase I (CamKI)	10.49
X69699	Hs.73149	PAX8, paired box gene 8	Member of the paired domain family of nuclear transcription factors; are involved in the ribosome assembly, required for normal thyroid development	10.39
AW382987	Hs.88474:42	Homo sapiens cDNA, mRNA sequence	Function unknown	10.21
AW957446	Hs.301711	Homo sapiens, clone MGC:23936 IMAGE:3838595, mRNA, complete cds	Function unknown	10.12
AA361562	Hs.178761	POH1: 26S proteasome-associated pad1 homolog	Ubiquitin-dependent protein degradation	10.01
AA834626		RAD54L, RAD54 (S.cerevisiae)-like	Has likely roles in mitotic and meiotic DNA recombination and repair; member of SNF2/SWI2 family of DNA-dependent ATPases	9.85
AI878927	Hs.79284	MEST, mesoderm specific transcript (mouse) homolog	Mesoderm specific protein; member of the alpha/beta hydrolase fold family	9.83
AW074266	Hs.23071	LOC85439: stonin 2	Stonin 2	9.74
NM_000947	Hs.74519	PRIM2A, primase, polypeptide 2A (58kD)	Subunit of DNA primase polypeptide 2A; part of the DNA polymerase alpha-primase complex	9.72

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	Ratio
NM_006187	Hs.56009	OAS3, 2'-5'-oligoadenylate synthetase 3 (100 kD)	Member of the 2'5'-oligoadenylate synthetase family	9.68
AW276858	Hs.81256	S100A4, S100 calcium binding protein A4 (calcium protein, calvasculin, metastasin, murine placental homolog)	Calcyclin (metastasis-associated) (S100 calcium-binding protein A4); Interacts with targets to link extracellular stimuli and cellular responses; member of the S100 family of tissue-specific calcium-binding proteins	9.66
T18997	Hs.180372	LOC139231: hypothetical protein BC016683	Function unknown	9.49
AA262294	Hs.180383	DUSP6, dual specificity phosphatase 6	Dual specificity protein phosphatase 6; selectively dephosphorylates and inactivates MAP kinase	9.48
AA220238	Hs.94986	RPP38: ribonuclease P (38kD)	Nucleus, ribonuclease P. Subunit p38 of ribonuclease P ribonucleoprotein; processes 5' ends of precursor tRNAs	9.41
AW505308	Hs.75812	PCK2, phosphoenolpyruvate carboxykinase 2 (mitochondrial)	Phosphoenolpyruvate carboxykinase 2; forms phosphoenolpyruvate by decarboxylation of oxaloacetate at the rate-limiting step of gluconeogenesis	9.38
AI186431	Hs.296638	PLAB: prostate differentiation factor	Macrophage inhibitory cytokine; member of a subgroup of the TGF-beta superfamily	9.12
AI095718	Hs.135015	Homo sapiens cDNA FLJ40906 fis, clone UTERU2004698, highly similar to Mus musculus mRNA for thrombospondin type 1 domain	Function unknown	9.04
W70171	Hs.75939	UMPK, uridine monophosphate kinase	The protein encoded by this gene catalyzes the phosphorylation of uridine monophosphate to uridine diphosphate. This is the first step in the production of the pyrimidine nucleoside triphosphates required for RNA and DNA synthesis. In addition, an allele of this gene may play a role in mediating nonhumoral immunity to Hemophilus influenzae type B.	8.97
AI580935	Hs.105698	Homo sapiens cDNA FLJ31553 fis, clone NT2RI2001178	Function unknown	8.90
AB040914	Hs.278628	ShrmL: Shroom-related protein	Shroom-related protein	8.87
AU076611	Hs.154672	MTHFD2, methylene tetrahydrofolate dehydrogenase (NAD+ dependent), methenyltetrahydrofolate cyclohydrolase	NAD-dependent methylene tetrahydrofolate dehydrogenase-cyclohydrolase; may provide formyltetrahydrofolate for formylmethionyl tRNA synthesis; involved in initiation of mitochondrial protein synthesis	8.71
AI089660	Hs.323401	LOC84661: dpy-30-like protein	dpy-30-like protein	8.71
D13666	Hs.136348:228,Hs.80988:2	OSF-2: osteoblast specific factor 2 (fasciclin I-like)	Cell adhesion, skeletal development. Putative bone adhesion protein; similar to the insect protein fasciclin I	8.64
AI798863	Hs.87191	ESTs	Function unknown	8.52

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	Ratio
U78093	Hs.15154	SRPX, sushi-repeat-containing protein, X chromosome	Putative membrane protein with short consensus repeat (sushi) domains	8.51
AI669760	Hs.188881	ESTs	Function unknown	8.37
AI375726	Hs.279918	MGC2198: hypothetical protein MGC2198	Function unknown	8.37
AW271106	Hs.133294	ESTs	Function unknown	8.30
AK001782	Hs.15093	HSPC195: hypothetical protein HSPC195	Function unknown	8.18
AF019226	Hs.8036	RAB3D,RAB3D, member RAS oncogene family	GTP-binding protein; are involved in vesicle transport; member of the RAB family of small GTPases	7.94
AW968343	Hs.24255	LOC150696: prominin-related protein	Prominin-related protein	7.90
AF111856	Hs.105039	SLC34A2, solute carrier family 34 (sodium phosphate), member 2	Sodium-dependent phosphate transporter; member of the renal type II co-transporter family	7.87
AA863360	Hs.26040	Homo sapiens, clone MGC:40051 IMAGE:5243005, mRNA,complete cds	Function unknown	7.75
NM_005764	Hs.271473	DD96: epithelial protein up-regulated in carcinoma, membrane associated protein 17	Up-regulated in malignant epithelial cells of renal cell carcinomas, and in carcinomas of colon, breast and lung	7.75
AW360901	Hs.183047	MGC4399: mitochondrial carrier protein	Mitochondrial carrier protein MGC4399	7.71
AL353944	Hs.50115	Homo sapiens mRNA; cDNA DKFZp761J1112 (from clone DKFZp761J1112)	Function unknown	7.69
H59799	Hs.42644	TXNL2, thioredoxin-like 2	Member of the thioredoxin family; has region of moderate similarity to glutaredoxin-like proteins	7.65
NM_002984	Hs.75703	CCL4, chemokine (C-C motif) ligand 4	Cytokine A4	7.64
AA642452	Hs.130881	BCL11A, B-cell CLL/lymphoma 11A (zinc finger protein)	May bind nucleic acids; contains three C2H2 type zinc finger domains	7.61
AA789081	Hs.4029	GAS41: glioma-amplified sequence-41	Similar to the transcription factors AF-9 and ENL	7.46
H13032	Hs.103378	MGC11034, hypothetical protein MGC11034	Function unknown	7.42
BE384836	Hs.3454	KIAA1821: KIAA1821 protein	KIAA1821 protein	7.40
AW067800	Hs.155223	STC2, stanniocalcin 2	Stanniocalcin 2; may regulate metal ion homeostasis and inhibits phosphate uptake	7.36
T55979	Hs.115474	RFC3, replication factor C (activator 1) 3 (38kD)	Subunit of replication factor C (activator 1) 3; activator of DNA polymerases	7.35
AJ278016	Hs.55565	ANKRD3, ankyrin repeat domain 3	Ortholog of mouse protien kinase C-associated kinase, putative gene, ankirin like, possible dual-specificity Ser/Thr/Tyr kinase domain	7.25

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	Ratio
		NM_025080:Homo sapiens hypothetical protein FLJ22316 (FLJ22316), mRNA. VERSION NM_025079.1 GI:13376631	Function unknown	7.22
AA084248	Hs.85339:64	GPR39, G protein-coupled receptor 39	GPR39, G protein-coupled receptor 39	7.15
BE620738	Hs.173125	PPIF, peptidylprolyl isomerase F (cyclophilin F)	Cyclophilin F (peptidylprolyl isomerase F); binds the immunosuppressant drug cyclosporin A	7.06
AF072873	Hs.114218	FZD6, frizzled (Drosophila) homolog 6	Frizzled-6; may function in tissue polarity, development and carcinogenesis; similar to frizzled receptor family, has seven transmembrane domains	7.04
AA852773	Hs.334838.	KIAA1866 protein	KIAA1866 protein	6.99
R07566	Hs.73817	CCL3, chemokine (C-C motif) ligand 3	Macrophage inflammatory protein 1 alpha; chemokine	6.98
NM_005211	Hs.174142	CSF1R, colony stimulating factor 1 receptor, formerly McDonough feline sarcoma viral (v-fms) oncogene homolog	Macrophage colony stimulating factor tyrosine kinase receptor; involved in regulation of growth and differentiation of myeloid cells	6.79
AI752666	Hs.76669	NNMT, nicotinamide N-methyltransferase	Nicotinamide N-methyltransferase; catalyzes the N-methylation of nicotinamide and other pyridines, structurally-related drugs and xenobiotics	6.52
AF182294	Hs.241576	LOC51691: U6 snRNA-associated Sm-like protein LSm8	Member of the Sm family; core constituent of snRNP complexes	6.50
AA457211	Hs.8858	BAZ1A, bromodomain adjacent to zinc finger domain, 1A	May bind DNA and act as a chromatin-mediated transcriptional regulator; contains a bromodomain and a PHD-finger	6.48
W40262	Hs.146310	zc79f02.s1 Pancreatic islet Homo sapiens cDNA clone IMAGE:328539 3', mRNA sequence	Function unknown	6.47
AB033091	Hs.74313	KIAA1265 protein	Function unknown	6.45
AA292998	Hs.163900	ESTs, Highly similar to winged helix/forkhead transcription factor [Homo sapiens] [H.sapiens]	Function unknown	6.36
BE613269	Hs.21893	DKFZp761N0624: hypothetical protein DKFZp761N0624	Function unknown	6.35
H25836	Hs.301527	ESTs, Moderately similar to unknown [Homo sapiens] [H.sapiens]	Function unknown	6.27
AL037228	Hs.82043	NUDT5, nudix (nucleoside diphosphate linked moiety X)-type motif 5	NDP-sugar hydrolase; converts ADP-ribose to AMP or ribose 5-phosphate; contains a MutT motif	6.25
AV662037	Hs.124740	FLJ30532: hypothetical protein FLJ30532	Function unknown	6.21

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	Ratio
AI674383	Hs.22891	wc38h08.x1 NCI_CGAP_Pr28 Homo sapiens cDNA clone IMAGE:2320959 3', mRNA sequence	Function unknown	6.20
AW342140	Hs.182545	ESTs, Weakly similar to POL2_MOUSE Retrovirus-related POL polyprotein [Contains: Reverse transcriptase ; Endonuclease] [M.musculus]	Function unknown	6.18
BE560135	Hs.5232	HSPC125, HSPC125 protein	Function unknown	6.17
BE409857	Hs.69499	HSPC132: hypothetical protein HSPC132	Moderately similar to a region of S. cerevisiae Ykl053c-ap	6.16
AW972542	Hs.289008	LOC116150: hypothetical protein, MGC:7199	Function unknown	6.16
AI523755	Hs.59236	DKFZP434L0718: hypothetical protein DKFZp434L0718	Function unknown	6.16
NM_014056	Hs.7917	DKFZP564K247: DKFZP564K247 protein	Function unknown	6.08
AI857607	Hs.181301	CTSS, cathepsin S	Cathepsin S; lysosomal cysteine (thiol) protease that cleaves elastin	6.04
AW247529	Hs.6793	PAFAH1B3, platelet-activating factor acetylhydrolase, isoform Ib, gamma subunit (29kD)	Platelet-activating factor acetylhydrolase gamma; may play a role in brain development	5.98
AK000868	Hs.5570	Homo sapiens cDNA FLJ10006 fis, clone HEMBA1000168, weakly similar to CYLICIN I	Function unknown	5.92
AF053551	Hs.31584	MTX2, metaxin 2	Very strongly similar to murine metaxin 2 (Mm.12941); are involved in mitochondrial protein import	5.91
AI538613	Hs.298241	TMPRSS3, Transmembrane protease, serine 3	The encoded protein contains a serine protease domain, a transmembrane domain, a LDL receptor-like domain, and a scavenger receptor cysteine-rich domain. This gene was identified as a tumor associated gene that is overexpressed in ovarian tumors.	5.86
U48508	Hs.89631	Human skeletal muscle ryanodine receptor gene (RYR1), exons 103, 104, 105, 106, and complete cds	Function unknown	5.86
T69387	Hs.76364	AIF1, allograft inflammatory factor 1	Allograft inflammatory factor 1; cytokine inducible protein associated with vascular injury	5.86
AC005954	Hs.25527	Homo sapiens chromosome 19, cosmid R28784, complete sequence	Function unknown	5.86
AB037805	Hs.88442	KIAA1384 protein	Function unknown	5.84

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	Ratio
AL031427	Hs.40094	Human DNA sequence from clone 167A19 on chromosome 1p32.1-33. Contains three genes for novel proteins, the DIO1 gene for type I iodothyronine deiodinase (EC 3.8.1.4, TXDI1, ITDI1) and an HNRNP A3 (Heterogenous Nuclear Ribonucleoprotein A3, FBRNP) pseudogene.	Function unknown	5.83
AA340864	Hs.278562	CLDN7, claudin 7	Similar to murine Cldn7; are an integral membrane protein	5.76
X89984	Hs.211563	BCL7A, B-cell CLL/lymphoma 7A	Similar to the actin-binding protein caldesmon; serine-rich	5.74
AI355761	Hs.242463	qt94a11.x1 NCI_CGAP_Co14 Homo sapiens cDNA clone IMAGE:1962908 3' similar to gb:X74929 KERATIN, TYPE II CYTOSKELETAL 8 (HUMAN);, mRNA sequence	Function unknown	5.73
AA376409	Hs.10862	Homo sapiens cDNA: FLJ23313 fis, clone HEP11919	Function unknown	5.71
AA310162	Hs.169248	HCS: cytochrome c	Somatic cytochrome c (heart cytochrome c)	5.67
AW015534	Hs.217493	ANXA2, annexin A2	Annexin II (lipocortin-2); enhances osteoclast formation and bone resorption; member of the annexin protein family	5.64
AA326108	Hs.53631:82	BHLHB3: basic helix-loop-helix domain containing, class B, 3	Basic helix-loop-helix (bHLH) transcription factors (e.g., DEC1, also called BHLHB2; 604256) are related to Drosophila hairy/enhancer of split proteins. They are involved in the control of proliferation and development during differentiation, particularly in neurons.	5.64
AA120865	Hs.23136	ESTs, Highly similar to THYA_HUMAN Prothymosin alpha [H.sapiens]	Function unknown	5.62
AK000517	Hs.6844	NALP2: NALP2 protein	Protein with low similarity to murine Op1	5.54
Z36842	Hs.57548	H.sapiens (xs85) mRNA, 209bp	Function unknown	5.53
AA831552	Hs.268016	Homo sapiens cDNA: FLJ21243 fis, clone COL01164		5.50
AL137578	Hs.27607	Homo sapiens mRNA; cDNA DKFZp564N2464 (from clone DKFZp564N2464)	Function unknown	5.50
AA316181	Hs.61635	STEAP, six transmembrane epithelial antigen of the prostate	Six transmembrane epithelial antigen of the prostate; prostate-specific cell-surface antigen	5.46

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	Ratio
X03635	Hs.1657	ESR1, estrogen receptor 1	Estrogen receptor; nuclear receptor transcription factor activated by ligand-binding, involved in hormone-mediated inhibition of gene expression	5.42
AI557280	Hs.184270	PT2.1_15_G11.r tumor2 Homo sapiens cDNA 3', mRNA sequence	Function unknown	5.41
AW248508	Hs.279727	Homo sapiens cDNA FLJ14035 fis, clone HEMBA1004638	Function unknown	5.40
N90866	Hs.276770	CDW52, CDW52 antigen (CAMPATH-1 antigen)	CAMPATH-1 antigen; GPI-anchored protein	5.39
U83115	Hs.161002	AIM1, absent in melanoma 1	Member of the beta gamma-crystallin superfamily of proteins; interactions with the cytoskeleton	5.35
AB007860	Hs.12802	DDEF2, development and differentiation enhancing factor 2	GTPase-activating protein; interacts with members of the Arf and Src family	5.35
Z46223	Hs.176663	H.sapiens DNA for immunoglobulin G Fc receptor IIIB	Immunoglobulin G Fc receptor	5.31
BE264974	Hs.6566	TRIP13; thyroid hormone receptor interactor 13	Interacts with ligand binding domain of thyroid hormone receptor and with human papillomavirus type 16 (HPV16) E1	5.30
AA194422	Hs.22564	MYO6, myosin VI	Motor, hearing, myosin ATPase, structural protein. Class 6 myosin; motor protein; very strongly similar to murine Myo6	5.27
AF134157	Hs.169487	MAFB, v-maf musculoaponeurotic fibrosarcoma oncogene homolog B (avian)	Very strongly similar to murine Krml; may function as a basic domain-leucine zipper transcription factor	5.25
AA232119	Hs.16085	SH120: putative G-protein coupled receptor	putative G-protein coupled receptor	5.25
W58353	Hs.285123	OSBPL10, oxysterol binding protein-like 10	Member of the oxysterol-binding protein (OSBP) family; may bind oxygenated derivatives of cholesterol	5.21
AW167128	Hs.231934	ESTs, Weakly similar to A57717 transcription factor EC2 - human [H.sapiens]	Function unknown	5.19
U70370	Hs.84136	PITX1, paired-like homeodomain transcription factor 1	Member of the homeodomain family of DNA binding proteins; may regulate gene expression and control cell differentiation	5.18
N55669	Hs.333823	MRPL13, mitochondrial ribosomal protein L13	Protein of the large 60S ribosomal subunit	5.17
BE298446	Hs.305890	BCL2L1, BCL2-like 1	BCL2-related protein; alternative form bcl-xlong inhibits apoptosis and bcl-xshort induces apoptosis	5.17
AW136551	Hs.181245	Homo sapiens cDNA FLJ12532 fis, clone NT2RM4000200	Function unknown	5.15
AW250380	Hs.109059	HGS, hepatocyte growth factor-regulated tyrosine kinase substrate	Zinc-finger protein; interacts with STAM, undergoes tyrosine phosphorylation in response to IL2, CSF2, or HGF	5.13

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	Ratio
AW002565	Hs.124660	Homo sapiens cDNA: FLJ21763 fis, clone COLF6967	Function unknown	5.13
AI697274	Hs.105435	GMDS, GDP-mannose 4,6-dehydratase	GDP-mannose-4,6-dehydratase; epimerase converts GDP-mannose to GDP-mannose-4-keto-6-D-deoxymannose, plays a role in the synthesis of fucosylated oligosaccharides	5.11
NM_003878	Hs.78619	GGH, gamma-glutamyl hydrolase (conjugase, folylpolygammaglutamyl hydrolase)	Gamma-glutamyl hydrolase; has greater exopeptidase activity on methotrexate pentaglutamate than on diglutamate	5.11
AF052112	Hs.12540	LYPLA1, lysophospholipase I	Lysophospholipid-specific lysophospholipase 1; hydrolyzes lysophosphatidyl choline	5.09
AV654694	Hs.82316	IFI44, interferon-induced protein 44	Member of the family of interferon-alpha/beta inducible proteins; may mediate the antiviral action of interferon	5.09
R24601		Homo sapiens adenylosuccinate synthetase isozyme (ADSS) mRNA, complete cds	Adenylosuccinate synthetase	5.07
BE019020	Hs.85838	Homo sapiens cDNA clone IMAGE:2963945 5' similar to TR:O15427 O15427 MONOCARBOXYLATE TRANSPORTER. ;, mRNA sequence	Function unknown	5.04
AW163799	Hs.198365	BPGM, 2,3-bisphosphoglycerate mutase	2,3-bisphosphoglycerate mutase; has synthase, mutase, and phosphatase activities, controls 2,3-diphosphoglycerate metabolism, which is an effector for haemoglobin	5.04
AA278921	Hs.1908	PRG1, proteoglycan 1, secretory granule	Secretory granule proteoglycan 1	5.02
NM_003726	Hs.19126	SCAP1, src family associated phosphoprotein 1	Src kinase-associated phosphoprotein; acts as an adaptor protein; contains a pleckstrin homology domain and an SH3 domain	5.02
AA281167	Hs.111911	ESTs, Weakly similar to T06291 extensin homolog T9E8.80 - Arabidopsis thaliana [A.thaliana]	Function unknown	5.02
		C9000306*:gi|12737280|ref|XP_006682.2| keratin 18 [Homo sapiens]||6633	Function unknown	5.01
AF098158	Hs.9329	C20orf1, chromosome 20 open reading frame 1	Proliferation-associated nuclear protein; associates with the spindle pole and mitotic spindle during mitosis	5.00

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	Ratio
AA101043	Hs.151254:19	KLK7, kallikrein 7 (chymotryptic; stratum corneum)	Epidermal differentiation. Stratum corneum chymotryptic enzyme; serine protease. Growing evidence suggests that many kallikreins are implicated in carcinogenesis and some have potential as novel cancer and other disease biomarkers. Thought to be involved in the proteolysis of intercellular cohesive structures preceding desquamation, which is the shedding of the outermost layer of the epidermis.	4.87
AF017986	Hs.31386:185	Homo sapiens secreted apoptosis related protein 1 (SARP1) mRNA, partial cds.	Function unknown	4.12
AW960564	Hs.3337:137	TM4SF1: transmembrane 4 superfamily member 1	Pathogenesis, plasma membrane, cell proliferation, N-linked glycosylation, integral membrane protein, integral plasma membrane protein. L6 antigen; member of the transmembrane 4 superfamily (TM4SF). The proteins mediate signal transduction events that play a role in the regulation of cell development, activation, growth and motility. This encoded protein is a cell surface antigen and is highly expressed in different carcinomas.	3.62
W29092	Hs.7678:40	CRABP1 Cellular retinoic acid binding protein 1	Cytoplasm, retinoid binding, signal transduction, developmental processes. Cellular retinoic acid-binding protein 1; are involved in delivering retinoic acid to the nucleus, assumed to play an important role in retinoic acid-mediated differentiation and proliferation processes.	3.34
H93366	Hs.7567:84	Homo sapiens cDNA: FLJ21962 fis, clone HEP05564	Function unknown	3.29
D49441	Hs.155981:53	MSLN, mesothelin	Cell adhesion, cell surface antigen, membrane. Pre-pro-megakaryocyte potentiating factor. An antibody that reacts with ovarian cancers and mesotheliomas was used to isolate a cell surface antigen named mesothelin. Although the function of mesothelin is unknown, it may play a role in cellular adhesion and is present on mesothelium, mesotheliomas, and ovarian cancers.	3.14
AA214228	Hs.127751:21,Hs.78006:5	C20orf180: chromosome 20 open reading frame 180	Region of high similarity to tyrosine-phosphorylated protein DOK1	2.99
M31126	Hs.272620:1	PSG9: pregnancy specific beta-1-glycoprotein 9	Pregnancy, extracellular, plasma glycoprotein. Member of the pregnancy-specific glycoprotein (PSG) and CEA families.	2.82
U62801	Hs.79361:65	KLK6, kallikrein 6 (neurosin, zyme)	Serine type peptidase, pathogenesis. Neurosin (protease M, zyme); a serine protease that cleaves amyloid precursor protein (APP). Growing evidence suggests that many kallikreins are implicated in carcinogenesis and some have potential as novel cancer and other disease biomarkers.	2.77
AK001536	Hs.285803:6	Homo sapiens cDNA FLJ12852 fis, clone NT2RP2003445	Function unknown	2.73

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	Ratio
NM_014767	Hs.74583:140	KIAA0275: KIAA0275 gene product	Function unknown	2.72
NM_000699	Hs.75733:129,Hs.278399:100,Hs.274376:1	AMY2A: amylase, alpha 2A; pancreatic	Alpha-amylase, extracellular space, carbohydrate metabolism. Pancreatic alpha-amylase 2A (1,4-alpha-D-glucan glucanohydrolase); cleaves internal a-1,4 bonds between glucose monomers to digest starch.	2.71
AA430348	Hs.288837:40	Homo sapiens cDNA FLJ12927 fis, clone NT2RP2004743	Function unknown	2.69
X51630	Hs.1145:22,Hs.296851:1	WT1, Wilms tumor 1	Nucleus, transcription factor, transcription regulation. 4 Zn finger domains. Functions in kidney and gonad proliferation and differentiation. Mutations in this gene are associated with the development of Wilms tumors in the kidney or with abnormalities of the genitourinary tract.	2.58
BE393948	Hs.50915:17	KLK5, kallikrein 5	Serine type peptidase, epidermal differentiation, extracellular space. Stratum corneum tryptic enzyme (kallikrein-like protein); may function in epidermal stratum corneum desquamation and turnover. Expression in prostate cancer negatively correlated with cancer aggressiveness (Yousef 2002)	2.34
NM_002776	Hs.69423:46	KLK10, kallikrein 10	Putative serine protease. Expressed in normal breast tissue and benign lesions, with loss of expression during tumor progression (Dhar 2001). SNPs associated with prostate, breast, testicular, and ovarian cancers (Bharaj 2002).	2.24
NM_000954	Hs.8272:294	PTGDS: prostaglandin D2 synthase (21kD, brain)	Membrane, prostaglandin-D synthase. Glutathione-independent prostaglandin D2 synthase; membrane associated, catalyzes synthesis of prostaglandin D; member of the lipocalin family of transporters.	2.15
AB029000	Hs.70823:109,Hs.297970:48	KIAA1077: sulfatase FP	Function unknown	2.04
AL044315	Hs.173094:70	KIAA1750; KIAA1750 protein	Function unknown	0.95
AA334592	Hs.79914:337	LUM: lumican	Vision, proteoglycan, extracellular matrix, cartilage condensation, extracellular matrix glycoprotein. Member of the specialized collagens and SLRP_family	0.93
S79895	Hs.83942:248	CTSK: cathepsin K (pycnodysostosis)	Lysosome, cathepsin K, cysteine-type peptidase, proteolysis and peptidolysis. Cathepsin K (cathepsin O), a cysteine (thiol) protease; involved in bone remodeling and reabsorption	0.91
AI091195	Hs.65029:120	Homo sapiens cDNA clone IMAGE:1566910 3', mRNA sequence	Function unknown	0.91

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	Ratio
AF026692; NM_003014	Hs.105700:83,Hs.278611:3	SFRP4: secreted frizzled-related protein 4	Member of the SFRP family that contains a cysteine-rich domain homologous to the putative Wnt-binding site of Frizzled proteins. SFRPs act as soluble modulators of Wnt signaling. The expression of SFRP4 in ventricular myocardium correlates with apoptosis related gene expression.	0.73
AI683243	Hs.97258:15	ESTs, Moderately similar to S29539 ribosomal protein L13a, cytosolic	Function unknown	-2.96
AI287700	Hs.111128:7	Homo sapiens, clone IMAGE:4106329, mRNA	Function unknown	-5.71
AA291377	Hs.50831:23	Homo sapiens Ly-6 antigen/uPA receptor-like domain-containing protein mRNA, complete cds	Function unknown	-6.78
AI420213	Hs.149722:3	cDNA clone IMAGE:2094208 3', mRNA sequence	Function unknown	-8.52
AJ245671	Hs.12844:73	EGFL6, EGF-like-domain; multiple 6	Cell cycle, oncogenesis, integrin ligand, extracellular space. Member of the epidermal growth factor (EGF) repeat superfamily; contains an EGF-like-domain. Expressed early during development, and its expression has been detected in lung and meningioma tumors.	-9.44
AB018305	Hs.5378:149	SPON1, spondin 1, (f-spondin) extracellular matrix protein	Extracellular matrix protein. Very strongly similar to rat F-spondin (Rn.7546); may have a role in the growth and guidance of axons.	-12.55
AW872527	Hs.59761:19	ESTs; Weakly similar to DAP1_HUMAN DEATH-ASSOCIATED PROTEIN 1	Function unknown	-14.17
AF129755	Hs.117772:9,Hs.88474:1	Homo sapiens prostaglandin endoperoxide H synthase-1 mRNA, partial 3' untranslated region.	Function unknown	-21.34
AI023799	Hs.163242:5	Homo sapiens cDNA clone IMAGE:1655725 3' similar to contains MER20.t2 MER20 repetitive element ;, mRNA sequence	Function unknown	-41.34

Table 3
Preferred diagnostic and prognostic markers for detecting ovarian cancer or a recurrence thereof or survival of a subject suffering from ovarian cancer

A. DOWN-REGULATED GENES

Accession Number	Unigene Mapping	Gene Name	Function	SEQ ID NO:	Chromosome Location	P value
AI631024; NM_005460	Hs.24948:32; Hs.300445:4	SNCAIP, synuclein, alpha interacting protein (synphilin)	Cytoplasm, pathogenesis, protein binding. Synphilin-1; promotes formation of cytosolic inclusions in neurons (SNCAIP). Synuclein alpha interacting protein contains several protein-protein interaction domains and interacts with alpha synuclein in neurons. Mutations of SNCAIP have been linked to Parkinson disease.	SEQ ID NO: 1 (DNA) SEQ ID NO: 2 (PRT)	5q23.2	0
NM_002387	Hs.1345:5	MCC, mutated in colorectal cancers	Receptor, signal transduction, tumor suppressor. Similar to the G protein-coupled m3 muscarinic acetylcholine receptor. MCC is a candidate for the putative colorectal tumor suppressor gene. The MCC gene product are involved in early stages of colorectal neoplasia in both sporadic and familial tumors.	SEQ ID NO: 3 (DNA) SEQ ID NO: 4 (PRT)	5q22.2	0
AI420582; NM_022117	Hs.136164:23	SE20-4, cutaneous T-cell lymphoma-associated tumor antigen se20-4se20-4	Cutaneous T-cell lymphoma-associated tumor antigen se20-4se20-4; differentially expressed nucleolar TGF-beta1 target protein (DENTT); also known as CDA1	SEQ ID NO: 5 (DNA) SEQ ID NO: 6 (PRT)	unmapped	0

Table 3 continued

Accession Number	Unigene Mapping	Gene Name	Function	SEQ ID NO:	Chromosome Location	P value
B. UP-REGULATED GENES						
BC006428; NM_016463	Hs.15093:210,Hs.280304:1	HSPC195, hypothetical protein HSPC195	Homo sapiens cDNA FLJ10920 fis, clone OVARC1000384-resourcerer.	SEQ ID NO: 7 (DNA) SEQ ID NO: 8 (PRT)	5q31.2	0
NM_017697	Hs.24743:94	FLJ20171, hypothetical protein FLJ20171	contains 3 RNA recognition motifs	SEQ ID NO: 9 (DNA) SEQ ID NO: 10 (PRT)	8q22.1	0
AW630088; NM_001306	Hs.76550:164	MAL2	Mal2 T-cell differentiation protein; found thru interaction with TPD52 which is overexpressed in breast cancer; 4 TM are involved in vesicle transport	SEQ ID NO: 11 (DNA) SEQ ID NO: 12 (PRT)	8q24.12	0
NM_015238	Hs.21543:36	KIAA0869, KIAA0869 protein; KIBRA	Function unknown	SEQ ID NO: 13 (DNA) SEQ ID NO: 14 (PRT)	5q34	0.0002
AA284679	Hs.25640:264,Hs.5372:2	CLDN3, claudin 3	Integral plasma membrane protein, pathogenesis, tight junction, transmembrane receptor. Member of the claudin family of integral membrane proteins; receptor for Clostridium perfringens enterotoxin;	SEQ ID NO: 15 (DNA) SEQ ID NO: 16 (PRT)	7q11.23	0.0004
NM_022454	Hs.97984:22	SOX17, SRY (sex determining region Y)-box 17	Likely ortholog of mouse SRY-box containing gene 17; alias SOX17	SEQ ID NO: 17 (DNA) SEQ ID NO: 18 (PRT)	8q11.23	0.0005
NM_005682	Hs.6527:201	GPR56, G protein-coupled receptor 56	cell adhesion, cell-cell signalling, G-protein linked receptor, integral plasma membrane protein, G-protein linked receptor protein signalling pathway. Member of the G protein-coupled receptor family; similar to secretin and calcitonin receptors. 7 transmembrane domains, a mucin-like domain and cysteine box in the N-terminal region. Expressed in range of tissues, highest levels in thyroid, selectively within the monolayer of cuboidal epithelial cells of the smaller, more actively secreting follicles of human thyroid. Differentially expressed in melanoma cell lines with different metastatic potential (Zendman et al 1999).	SEQ ID NO: 19 (DNA) SEQ ID NO: 20 (PRT)	16q13	0.0012
NM_001307	Hs.278562:101	CLDN7, claudin 7	Integral membrane protein, tight junction. Similar to murine Cldn7;	SEQ ID NO: 21 (DNA) SEQ ID NO: 22 (PRT)	17p13.1	0.0016

NM_014736	Hs.81892:95	KIAA0101 gene product	function unknown; no signficant hits with Superfamily	SEQ ID NO: 23 (DNA) SEQ ID NO: 24 (PRT)	15q31	0.0025
BE184455; NM_003064	Hs.251754:128,Hs.245742:1	SLPI, secretory leukocyte protease inhibitor (antileukoproteinase)	Plasma protein, proteinase inhibitor. Secreted inhibitor which protects epithelial tissues from serine proteases. Found in various secretions including seminal plasma, cervical mucus, and bronchial secretions, has affinity for trypsin, leukocyte elastase, and cathepsin G. Its inhibitory effect contributes to the immune response by protecting epithelial surfaces from attack by endogenous proteolytic enzymes; the protein is also thought to have broad-spectrum anti-biotic activity.	SEQ ID NO: 25 (DNA) SEQ ID NO: 26 (PRT)	20q13.12	0.0034
NM_013994	Hs.75562:147	DDR1, discoidin domain receptor family, member 1	Cell adhesion, integral plasma membrane protein, transmembrane receptor, protein tyrosine kinase. Epithelial-specific receptor protein tyrosine kinase; are involved in cell adhesion; has putative discoidin motifs in extracellular domain. DDR1 (CD167a) is a RTK that is widely expressed in normal and transformed epithelial cells and is activated by various types of collagen.	SEQ ID NO: 27 (DNA) SEQ ID NO: 28 (PRT)	6p21.33	0.0055
NM_001067	Hs.156346:184,Hs.270810:2	TOP2A, topoisomerase (DNA) II alpha (170kD)	DNA binding, DNA topoisomerase (ATP-hydrolyzing), nucleus. DNA topoisomerase II alpha; may relax DNA torsion upon replication or transcription. Involved in processes such as chromosome condensation, chromatid separation, and the relief of torsional stress that occurs during DNA transcription and replication. Catalyzes the transient breaking and rejoining of two strands of duplex DNA. The gene encoding this enzyme functions as the target for several anticancer agents and a variety of mutations in this gene have been associated with the development of drug resistance. Reduced activity of this enzyme may also play a role in ataxia-telangiectasia.	SEQ ID NO: 29 (DNA) SEQ ID NO: 30 (PRT)	17q21.2	0.006

BE386983; NM_138410	Hs.343214	CKLFSF7; chemokine-like factor super family 7	chemokine-like factor gene superfamily; transmb 4 superfamily	SEQ ID NO: 31 (DNA) SEQ ID NO: 32 (PRT)	3p23	0.0131
AF098158; NM_012112	Hs.9329:152	C20orf1, chromosome 20 open reading frame 1	ATP binding, GTP binding, cell proliferation, mitosis, nucleus spindle. Proliferation-associated nuclear protein; associates with the spindle pole and mitotic spindle during mitosis	SEQ ID NO: 33 (DNA) SEQ ID NO: 34 (PRT)		0.0183
NM_001769	Hs.1244:227,Hs.230559:1,Hs.242020:1	CD9: CD9 antigen (p24)	Plasma membrane, integral plasma membrane protein. Member of the transmembrane 4 superfamily (TM4SF); may mediate platelet activation and aggregation. Cell surface glycoprotein that is known to complex with integrins and other transmembrane 4 superfamily proteins.	SEQ ID NO: 35 (DNA) SEQ ID NO: 36 (PRT)	12p13.31	0.0006
NM_020859	Hs.278628:52	ShrmL, Shroom-related protein (KIAA1481 protein)	Amiloride-sensitive sodium channel (weakly similar to Mus musculus PDZ domain actin binding protein)	SEQ ID NO: 37 (DNA) SEQ ID NO: 38 (PRT)		0.0074
NM_004433	Hs.166096:170	ELF3, E74-like factor 3 (ets domain transcription factor, epithelial-specific)	Embryogenesis and morphogenesis, transcription co-activator, transcription factor, transcription from Pol II promoter. ETS domain transcriptional activator; activates expression of epithelial cell specific genes.	SEQ ID NO: 39 (DNA) SEQ ID NO: 40 (PRT)	1q32.1	0.0004
AI791905; NM_019027	Hs.95549:147,Hs.229556:1	FLJ20273, RNA-binding protein	Contains four RNA recognition motifs (RRM, RBD, or RNP)	SEQ ID NO: 41 (DNA) SEQ ID NO: 42 (PRT)		0.0007
X69699; NM_013952	Hs.73149:72,Hs.213008:1	PAX8, paired box gene 8	Histogenesis and organogenesis, embryogenesis and morphogenesis, thyroid-stimulating hormone receptor, transcription factor. Member of the paired domain family of nuclear transcription factors; are involved in the ribosome assembly, required for normal thyroid development. PAX genes play critical roles during fetal development and cancer growth.	SEQ ID NO: 43 (DNA) SEQ ID NO: 44 (PRT)	2q13	0.0009
AI301558	Hs.290801:35, Hs.356228	EST	Function unknown	SEQ ID NO: 45 (DNA)		0.0044
NM_018000	Hs.79741:18	FLJ10116, hypothetical protein FLJ10116	Function unknown	SEQ ID NO: 46 (DNA) SEQ ID NO: 47 (PRT)	2q35	0.0051
NM_144724	Hs.124740:18	hypothetical protein FLJ30532	59% identity to human Zinc finger protein 91	SEQ ID NO: 48 (DNA) SEQ ID NO: 49 (PRT)	5q13.12	0.0051

AF111856; NM_006424	Hs.105039:48	SLC34A2, solute carrier family 34 (sodium phosphate), member 2	SLC34A2: solute carrier family 34 (sodium phosphate), member 2; contains 8 predicted TMs and a cysteine-rich N-terminal region. Type 2 sodium-dependent phosphate transporter. member of the renal type II co-transporter family.	SEQ ID NO: 50 (DNA) SEQ ID NO: 51 (PRT)	4p15.2	0.0121
AW959311	Hs.87019:8; Hs.172012	EST DKFZp434J037	probable serine/threonine protein kinase; KIAA0537	SEQ ID NO: 52 (DNA)	1q32.1	0.0251
AF111713	Hs.286218:64	JAM1, junctional adhesion molecule	Cell motility, inflammatory response, intercellular junction. Role in the regulation of tight junction assembly in epithelia. Ligation of JAM is required for reovirus-induced activation of NF-kappa-B and apoptosis. Role in lymphocyte homing.	SEQ ID NO: 53 (DNA) SEQ ID NO: 54 (PRT)		0.0261
AU076611; NM_006636	Hs.154672:123	MTHFD2, methylene tetrahydrofolate dehydrogenase (NAD+ dependent); methenyltetrahydr ofolate cyclohydrolase	Electron transporter, methenyltetrahydrofolate cyclohydrolase, mitochondrion. encodes a nuclear-encoded mitochondrial bifunctional enzyme with methylenetetrahydrofolate dehydrogenase and methenyltetrahydrofolate cyclohydrolase activities. may provide formyltetrahydrofolate for formylmethionyl tRNA synthesis; involved in initiation of mitochondrial protein synthesis.	SEQ ID NO: 55 (DNA) SEQ ID NO: 56 (PRT)	2p13.1	0.0342

Table 3 continued

Accession Number	Unigene Mapping	Gene Name	Function	SEQ ID NO:	Chromosome Location	P value
C. UP-REGULATED GENES IN MUCINOUS OVARIAN CANCER ONLY						
AA584890; NM_006149	Hs.5302:132	LGALS4, lectin, galactoside-binding, soluble, 4 (galectin 4)	Lectin, cytosol, cell adhesion, plasma membrane. Binds to beta galactoside, involved in cell adhesion, cell growth regulation, inflammation, immunomodulation, apoptosis and metastasis; member of a family of lectins. LGALS4 is an S-type lectin that is strongly underexpressed in colorectal cancer.	SEQ ID NO: 57 (DNA) SEQ ID NO: 58 (PRT)	19q13.2	0.0001
	Hs.89436:50	CDH17, cadherin 17, LI cadherin (liver-intestine)	Cell adhesion, integral plasma membrane protein, membrane fraction, small molecule transport, transporter. Member of the cadherin family of calcium-dependent glycoproteins; facilitates uptake of peptide-based drugs, may mediate cell-cell interactions. Component of the gastrointestinal tract and pancreatic ducts, intestinal proton-dependent peptide transporter in the first step in oral absorption of many medically important peptide-based drugs.	SEQ ID NO: 59 (DNA) SEQ ID NO: 60 (PRT)	8q22.1	0.0172
NM_005588	Hs.179704	MEP1A, meprin A alpha, PABA peptide hydrolase	metalloprotease located apically and secreted by epithelial cells in normal colon; degrades broad range of ECM components in vitro; proposed role in tumour progression by facilitating migration, intravasation and metastasis	SEQ ID NO: 61 (DNA) SEQ ID NO: 62 (PRT)	6p12	0.01

Table 3 continued

Accession Number	Unigene Mapping	Gene Name	Function	SEQ ID NO:	Chromosome Location	P value
D. PROGNOSTIC MARKERS FOR SURVIVAL OR RECURRENCE						
NM_015092	Hs.278428	DD5; EDD	Homo sapiens progestin induced protein (DD5), mRNA. EDD; Soluble fraction, cell proliferation, ubiquitin--protein ligase, ubiquitin conjugating enzyme, ubiquitin-dependent protein degradation. Member of the HECT family of proteins; may function as an E3 ubiquitin-protein ligase. This gene is localized to chromosome 8q22, a locus disrupted in a variety of cancers. This gene potentially has a role in regulation of cell proliferation or differentiation.	SEQ ID NO: 63 (DNA) SEQ ID NO: 64 (PRT)	8q22.3	0.00
BE465867; NM_014992	Hs.197751:66	DAAM1	dishevelled associated activator of morphogenesis 1 The protein encoded by this gene contains FH domains and belongs to a novel FH protein subfamily implicated in cell polarity, thought to function as a scaffolding protein.	SEQ ID NO: 65 (DNA) SEQ ID NO: 66 (PRT)	14q23.1	0.04
AA381553; NM_002122	Hs.198253:21	HLA1QA	major histocompatibility complex, class II, DQ alpha 1 Pathogenesis, class II major histocompatibility complex antigen. Alpha 1 chain of HLA-DQ1 class II molecule (Ia antigen); complex binds peptides and presents them to CD4+ T lymphocytes|Proteome	SEQ ID NO: 67 (DNA) SEQ ID NO: 68 (PRT)	6p21.3	0.00
AF026692; NM_003014	Hs.105700:83,Hs. 278611:3	SFRP4: secreted frizzled-related protein 4	Member of the SFRP family that contains a cysteine-rich domain homologous to the putative Wnt-binding site of Frizzled proteins. SFRPs act as soluble modulators of Wnt signaling. The expression of SFRP4 in ventricular myocardium correlates with apoptosis related gene expression.	SEQ ID NO: 69 (DNA) SEQ ID NO: 70 (PRT)	7p14	0.73
AW015534; NM_004039	Hs.217493	ANXA2, annexin A2	Annexin II (lipocortin-2); enhances osteoclast formation and bone resorption; member of the annexin protein family	SEQ ID NO: 71 (DNA) SEQ ID NO: 72 (PRT)	15q21-22	0.00
BE24669; NM_003955	Hs.345728	SOCS3	STAT induced STAT-inhibitor 3; suppressor of cytokine signalling 3; suppression of IL-6 mediated signalling	SEQ ID NO: 73 (DNA) SEQ ID NO: 74 (PRT)	17q25.3	0.02
AI677897; NM_014059	Hs.76640	RGC32	RGC32, hypothetical protein, unknown function	SEQ ID NO: 75 (DNA) SEQ ID NO: 76 (PRT)	13q13.3	0.04

AA829286; NM_000331	Hs.332053	SAA1, serum amyloid A1	Serum amyloid A1; high density lipoapoprotein; role in cholesterol metabolism; inflammatory response	SEQ ID NO: 77 (DNA) SEQ ID NO: 78 (PRT)	11p15.1	0.04
AA243499; NM_018004	Hs.104800	FLJ10134, hypothetical protein	Unknown	SEQ ID NO: 79 (DNA) SEQ ID NO: 80 (PRT)	3q12.3	0.01
M86849; NM_004004	Hs.323733	GJB2, gap junction protein beta2; connexin 26	Cellular gap junctions; mutations cause some forms of deafness	SEQ ID NO: 81 (DNA) SEQ ID NO: 82 (PRT)	13q11-12	0.00
NM_002514	Hs.235935	NOV1; Nephroblastoma overexpressed gene	Role in cell adhesion and migration in endothelial cells; promotes cell survival	SEQ ID NO: 83 (DNA) SEQ ID NO: 84 (PRT)	8q24.1	0.01

Table 4

Correlation of expression between normal ovarian surface epithelium (OSE), non-invasive tumors (borderline, BL) and ovarian cancer (CA) as determined by ANOVA

	CA125	MUC-1	E-cadherin	CLDN3	Ep-CAM	SOX17
OSE vs IC	<0.0001	<0.0001	0.7251	0.6132	0.1573	0.0854
OSE vs. BL	0.1765	<0.0001	0.0307	0.3633	0.0005	0.2287
OSE vs. CA	0.5443	<0.0001	0.1687	0.0008	<0.0001	0.6900
IC vs. BL	<0.0001	<0.0001	0.1116	0.7849	0.0913	0.2530
IC vs. CA	<0.0001	0.2707	0.4147	0.0071	0.0002	0.0544
BL vs. CA	0.0001	<0.0001	0.0615	<0.0001	0.0011	0.0152

Table 5

Correlation of gene expression with patient outcome (univariate analysis ie., expression alone without the influence of covariates)

Univariate analysis for clinicopathological variables and CLDN3, Ep-CAM, SOX17, CA125, MUC1 and E-cadherin immunoreactivity with survival and relapse in 156 patients with epithelial ovarian cancer

	Disease Specific Survival		Relapse Free Survival	
Variable	Univariate Hazards ratio (95% CI)	p-value	Univariate Hazards ratio (95% CI)	p-value
Pathological tumor stage				
Stage 1 - 3b *vs.* 3c - 4b	5.89 (3.214-10.79)	**<0.0001**	7.37 (3.26-16.63)	**<0.0001**
Tumor grade				
BL and G1 *vs.* G2 and G3	5.508 (2.745-11.052)	**<0.0001**	7.02 (2.76-17.82)	**<0.0001**
Age				
<50 *vs.* >=50	0.533 (0.288-0.988)	**0.0458**	0.62 (0.29-1.33)	0.2221
Residual Disease				
RD<1cm *vs.* >=1cm	4.192 (2.671-6.580)	**<0.0001**	4.17 (2.30-7.55)	**<0.0001**
CA125 level at diagnosis				
CA125 <500 *vs.* >500 U/ml	1.843 (1.102-3.080)	**0.0197**	2.292 (1.19-4.40)	**0.0128**
Performance Status				
PS<1 *vs.* >1	0.270 (0.133-0.549)	**0.0003**	0.53 (0.16-1.74)	0.2965
CLDN3 expression				
Membranous Score 0 *vs.* >0	2.794 (1.012-7.718)	**0.0474**	2.521 (0.908-6.998)	0.0758
Membranous Score <1 *vs.* >1	1.309 (0.763-2.246)	0.3285	1.952 (1.103-3.457)	**0.0217**
Ep-CAM expression				
Membranous Score <1 *vs.* >1	1.460 (0.809-2.634)	0.2093	2.041 (0.997-4.177)	0.0509
Membranous Score <2 *vs.* >2	1.041 (0.634-1.711)	0.873	1.449 (0.845-2.487)	0.1779
SOX17 expression				
Nuclear membranous Score 0 *vs.* >0	0.839 (0.514-1.368)	0.481	1.311 (0.728-2.358)	0.3667
Nuclear membranous Score <1 *vs.* >1	1.407 (0.615-3.218)	0.4183	1.037 (0.380-2.829)	0.9437
CA125 expression				
Membranous apical Score 0 *vs.* >0	2.581 (1.393-4.781)	**0.0026**	2.725 (1.218-6.093)	**0.0146**
Membranous apical Score <1 *vs.* >1	1.637 (1.045-2.564)	**0.0313**	1.298 (0.731-2.307)	0.3737
MUC1 expression				
Membranous apical Score 0 *vs.* >0	2.479 (0.343-17.898)	0.368	NA	
Membranous apical Score <1 *vs.* >1	3.745 (1.176-11.926)	**0.0254**	6.432 (1.562-26.483)	**0.0099**
Membranous apical Score <2 *vs.* >2	1.814 (0.898-3.664)	0.0969	3.893 (1.552-9.766)	**0.0038**
E-cadherin expression				
Membranous Score 0 *vs.* >0	0.806 (0.493-1.318)	0.3892	0.837 (0.477-1.467)	0.5341
Membranous Score <1 *vs.* >1	1.331 (0.532-3.333)	0.5411	0.847 (0.263-2.731)	0.7814
Membranous Score <2 *vs.* >2	0.593 (0.082-4.284)	0.6041	0.913 (0.125-6.646)	0.9284

Table 6

Correlation of gene expression with patient outcome (multivariate analysis ie looking at expression incorporating the influence of covariates)

Multivariate analysis for univariate significant clinicopathological variables and CLDN3, Ep-CAM, SOX17, CA125, MUC1 and E-cadherin immunoreactivity with survival and relapse in 156 patients with epithelial ovarian cancer

	Disease Specific Survival		Relapse Free Survival	
Variable	Multivariate Hazards ratio (95% CI)	p-value	Univariate Hazards ratio (95% CI)	p-value
Pathological tumor stage				
Stage 1 - 3b vs. 3c - 4b	5.66 (2.467-13.012)	**<0.0001**	5.192 (1.860-14.496)	**0.0017**
Tumor grade				
BL and G1 vs. G2 and G3	4.919 (2.080-11.633)	**0.0003**	7.989 (2.385-26.760)	**0.0008**
Age				
<50 vs. >=50	0.951 (0.482-1.877)	0.8853		
Residual Disease				
RD<1cm vs. >=1cm	2.974 (1.783-4.959)	**<0.0001**	2.779 (1.433-5.393)	**0.0025**
CA125 level at diagnosis				
CA125 <500 vs. >500 U/ml	1.148 (0.625-2.109)	0.6563	1.289 (0.659-2.520)	0.4587
Performance Status				
PS<1 vs. >1	0.286 (0.136-0.601)	**0.0009**		
CLDN3 expression				
Membranous Score 0 vs. >0	1.165 (0.325-4.183)	0.8145		
Membranous Score <1 vs. >1			0.953 (0.473-1.919)	0.8918
CA125 expression				
Membranous apical Score 0 vs. >0	0.917 (0.415-2.025)	0.8302	0.693 (0.271-1.768)	0.4427
Membranous apical Score <1 vs. >1	1.664 (0.976-2.837)	**0.0612**		
MUC1 expression				
Membranous apical Score 0 vs. >0				
Membranous apical Score <1 vs. >1	0.678 (0.255-1.804)	0.4361		
Membranous apical Score <2 vs. >2				

WE CLAIM:

1. A method of detecting an ovarian cancer-associated transcript in a biological sample, the method comprising contacting the biological sample with a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Table 1 or 2 or 3.

2. A method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein a modified level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has an ovarian cancer, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

(i) a sequence comprising at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 46, 48, 50, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;

(ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 46, 48, 50, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;

(iii) a sequence that is at least about 80% identical to a sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 46, 48, 50, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;

(iv) a sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 47, 49, 51, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82 and 84; and

(v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

3. A method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein a modified level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has an ovarian cancer, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

(i) a sequence comprising at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 1, 5, 7, 9, 11, 13, 15, 17, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 45, 46, 48, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;

(ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 1, 5, 7, 9, 11, 13, 15, 17, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 45, 46, 48, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;

(iii) a sequence that is at least about 80% identical to a sequence selected from the group consisting of SEQ ID NOs: 1, 5, 7, 9, 11, 13, 15, 17, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 45, 46, 48, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;

(iv) a sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 6, 8, 10, 12, 14, 16, 18, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 47, 49, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82 and 84; and

(v) a sequence that is complementary to (i) or (ii) or (iii) or (iv).

4. The method of claim 2 or 3 wherein the hybridization is enhanced in the sample from the subject being tested compared to the hybridization obtained for a sample from a control subject not having ovarian cancer.

5. The method of claim 2 or 3 wherein the hybridization is reduced in the sample from the subject being tested compared to the hybridization obtained for a sample from a control subject not having ovarian cancer.

6. A method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein an enhanced level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has an ovarian ovarian cancer, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

(i) a sequence comprising at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 or 2 other than a nucleic acid having an Accession Number selected from the group consisting of NM_022117, NM_005460, NM_002387, AI745249 and AI694200;

(ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 or 2 other than a nucleic acid having an Accession Number selected from the group consisting of NM_022117, NM_005460, NM_002387, AI745249 and AI694200;

(iii) a sequence that is at least about 80% identical to (i) or (ii);

(iv) a sequence that encodes a polypeptide encoded by a nucleic acid set forth in Table 1 or 2 other than a nucleic acid having an Accession Number selected from the group consisting of NM_022117, NM_005460, NM_002387, AI745249 and AI694200; and

(v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

7. The method of claim 6 wherein the nucleic acid probe comprises a sequence selected from the group consisting of:

(i) a sequence comprising at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 7, 9, 11, 13, 15, 17, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 45, 46, 48, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;

(ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 7, 9, 11, 13, 15, 17, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 45, 46, 48, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;

(iii) a sequence that is at least about 80% identical to a sequence selected from the group consisting of SEQ ID NOs: 7, 9, 11, 13, 15, 17, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 45, 46, 48, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;

(iv) a sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 10, 12, 14, 16, 18, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 47, 49, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82 and 84; and

(v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

8. A method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein a reduced level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has an ovarian ovarian cancer, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

(i) a sequence comprising at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of NM_022117, NM_005460, NM_002387, AI745249 and AI694200;

(ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of NM_022117, NM_005460, NM_002387, AI745249 and AI694200;

(iii) a sequence that is at least about 80% identical to (i) or (ii);

(iv) a sequence that encodes a polypeptide encoded by a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of NM_022117, NM_005460, NM_002387, AI745249 and AI694200; and

(v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

9. The method of claim 8 wherein the nucleic acid probe comprises a sequence selected from the group consisting of:

(i) a sequence comprising at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 1, 3, and 5;

(ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 1, 3, and 5;

(iii) a sequence that is at least about 80% identical to a sequence selected from the group consisting of SEQ ID NOs: 1, 3, and 5;

(iv) a sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, and 6; and

(v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

10. The method according to any one of claims 1 to 9 wherein the ovarian cancer that is diagnosed is an epithelial ovarian cancer.

11. The method according to any one of claims 1 to 9 wherein the ovarian cancer that is diagnosed is selected from the group consisting of serous ovarian cancer, non-invasive ovarian cancer, mixed phenotype ovarian cancer, mucinous ovarian cancer, endometrioid ovarian cancer, clear cell ovarian cancer, papillary serous ovarian cancer, Brenner cell and undifferentiated adenocarcinoma.

12. The method according to claim 11 wherein the ovarian cancer that is diagnosed is selected from the group consisting of serous ovarian cancer, mucinous ovarian cancer, endometrioid ovarian cancer and clear cell ovarian cancer.

13. A method of diagnosing a serous ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein a modified level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has a serous ovarian cancer, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

(i) a sequence comprising at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 2 or as set forth in Table 1 and having an Accession

Number selected from the group consisting of: U62801, D49441, X51630, And AB018305;

(ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 2 or as set forth in Table 1 and having an Accession Number selected from the group consisting of: U62801, D49441, X51630, And AB018305;

(iii) a sequence that is at least about 80% identical to (i) or (ii);

(iv) a sequence that encodes a polypeptide encoded by a nucleic acid set forth in Table 2 or as set forth in Table 1 and having an Accession Number selected from the group consisting of: U62801, D49441, X51630, And AB018305; and

(v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

14. A method of diagnosing a mucinous ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein an elevated level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has a mucinous ovarian cancer, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

(i) a sequence comprising at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: NM_006149, AA315933, U47732, NM_005588, AW503395, NM_004063, AI073913, AI928445, NM_022454, W40460, AA132961 and AF111856;

(ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: NM_006149, AA315933, U47732, NM_005588, AW503395, NM_004063, AI073913, AI928445, NM_022454, W40460, AA132961 and AF111856;

(iii) a sequence that is at least about 80% identical to (i) or (ii);

(iv) a sequence that encodes a polypeptide encoded by a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: NM_006149, AA315933, U47732, NM_005588, AW503395, NM_004063, AI073913, AI928445, NM_022454, W40460, AA132961 and AF111856; and

(v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

15. The method of claim 14 wherein the nucleic acid probe comprises a sequence selected from the group consisting of:

(i) a sequence comprising at least about 20 contiguous nucleotides from SEQ ID NO: 57 or 59 or 61;

(ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from SEQ ID NO: 57 or 59 or 61;

(iii) a sequence that is at least about 80% identical to SEQ ID NO: 57 or 59 or 61;

(iv) a sequence that encodes the amino acid sequence set forth in SEQ ID NO: 58 or 60 or 62; and

(v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

16. The method according to any one of claims 1 to 15 comprising performing a PCR reaction.

17. The method according to any one of claims 1 to 16 comprising performing a nucleic acid hybridization.

18. A method of detecting an ovarian cancer-associated polypeptide in a biological sample the method comprising contacting the biological sample with an antibody that binds specifically to an ovarian cancer-associated polypeptide in the biological sample, the polypeptide being encoded by a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-3.

19. A method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein a modified level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer indicates that the subject being tested has an ovarian cancer, and wherein said antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a sequence having at least about 80% identity to a sequence

selected from the group consisting of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 47, 49, 51, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82 and 84.

20. The method of claim 19 wherein the antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a sequence having at least about 80% identity to a sequence selected from the group consisting of SEQ ID NOs: 2, 6, 8, 10, 12, 14, 16, 18, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 47, 49, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82 and 84.

21. A method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein an enhanced level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer indicates that the subject being tested has an ovarian cancer, and wherein said antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a polypeptide encoded by a nucleic acid set forth in Table 1 or 2 other than a nucleic acid having an Accession Number selected from the group consisting of NM_022117, NM_005460, NM_002387, AI745249 and AI694200.

22. The method of claim 21 wherein the antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a sequence having at least about 80% identity to a sequence selected from the group consisting of SEQ ID NOs: 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 47, 49, 51, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82 and 84.

23. A method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein a reduced level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer indicates that the subject being tested has an ovarian cancer, and wherein said antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous

amino acid residues of a polypeptide encoded by a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of NM_022117, NM_005460, NM_002387, AI745249 and AI694200.

24. The method of claim 23 wherein the antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a sequence having at least about 80% identity to a sequence selected from the group consisting of SEQ ID NOs: 2, 4, and 6.

25. The method according to any one of claims 19 to 24 wherein the ovarian cancer that is diagnosed is an epithelial ovarian cancer.

26. The method according to any one of claims 19 to 24 wherein the ovarian cancer that is diagnosed is selected from the group consisting of serous ovarian cancer, non-invasive ovarian cancer, mixed phenotype ovarian cancer, mucinous ovarian cancer, endometrioid ovarian cancer, clear cell ovarian cancer, papillary serous ovarian cancer, Brenner cell and undifferentiated adenocarcinoma.

27. The method according to claim 26 wherein the ovarian cancer that is diagnosed is selected from the group consisting of serous ovarian cancer, mucinous ovarian cancer, endometrioid ovarian cancer and clear cell ovarian cancer.

28. A method of diagnosing a serous ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein a modified level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer indicates that the subject being tested has a serous ovarian cancer, and wherein said antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a polypeptide encoded by a nucleic acid set forth in Table 2 or as set forth in Table 1 and having an Accession Number selected from the group consisting of: U62801, D49441, X51630, And AB018305.

29. A method of diagnosing a mucinous ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject

being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein a reduced level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer indicates that the subject being tested has a mucinous ovarian cancer, and wherein said antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a polypeptide encoded by a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: NM_006149, AA315933, U47732, NM_005588, AW503395, NM_004063, AI073913, AI928445, NM_022454, W40460, AA132961 and AF111856.

30. The method according to claim 29 wherein the antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a sequence having at least about 80% identity to SEQ ID NO: 58 or 60 or 62.

31. A method of detecting an ovarian cancer-associated antibody in a biological sample the method comprising contacting the biological sample with a polypeptide encoded by a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-3, wherein the polypeptide specifically binds to the ovarian cancer-associated antibody.

32. The method according to any one of claims 1 to 31 wherein the biological sample is contacted with a plurality of nucleic acid probes and/or antibodies and/or polypeptides.

33. The method according to any one of claims 1 to 32 wherein the subject being tested is a patient undergoing a therapeutic regimen to treat ovarian cancer.

34. The method according to any one of claims 1 to 32 wherein the subject being tested is a subject suspected of having ovarian cancer.

35. A method of monitoring the efficacy of a therapeutic treatment of ovarian cancer, the method comprising:

(i) providing a biological sample from a patient undergoing the therapeutic treatment; and

(ii) determining the level of a ovarian cancer-associated transcript in the biological sample by contacting the biological sample with a polynucleotide

that selectively hybridizes to a sequence having at least about 80% identity to a sequence as shown in any one of Tables 1-3, thereby monitoring the efficacy of the therapy.

36. The method according to claim 35 further comprising comparing the level of the ovarian cancer-associated transcript to a level of the ovarian cancer-associated transcript in a biological sample from the patient prior to, or earlier in, the therapeutic treatment.

37. A method of monitoring the efficacy of a therapeutic treatment of ovarian cancer, the method comprising :

(i) providing a biological sample from a patient undergoing the therapeutic treatment; and

(ii) determining the level of a ovarian cancer-associated antibody in the biological sample by contacting the biological sample with a polypeptide encoded by a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-3, wherein the polypeptide specifically binds to the ovarian cancer-associated antibody, thereby monitoring the efficacy of the therapy.

38. The method of claim 37 further comprising comparing the level of the ovarian cancer-associated antibody to a level of the ovarian cancer-associated antibody in a biological sample from the patient prior to, or earlier in, the therapeutic treatment.

39. A method of monitoring the efficacy of a therapeutic treatment of ovarian cancer, the method comprising :

(i) providing a biological sample from a patient undergoing the therapeutic treatment; and

(ii) determining the level of a ovarian cancer-associated polypeptide in the biological sample by contacting the biological sample with an antibody, wherein the antibody specifically binds to a polypeptide encoded by a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-3, thereby monitoring the efficacy of the therapy.

40. The method of claim 39 further comprising comparing the level of the ovarian cancer-associated polypeptide to a level of the ovarian cancer-associated polypeptide in a biological sample from the patient prior to, or earlier in, the therapeutic treatment.

41. The method according to any one of claims 35 to 40 wherein the ovarian cancer that is diagnosed is an epithelial ovarian cancer.

42. The method according to any one of claims 35 to 41 wherein the ovarian cancer that is diagnosed is selected from the group consisting of serous ovarian cancer, non-invasive ovarian cancer, mixed phenotype ovarian cancer, mucinous ovarian cancer, endometrioid ovarian cancer, clear cell ovarian cancer, papillary serous ovarian cancer, Brenner cell and undifferentiated adenocarcinoma.

43. The method according to claim 42 wherein the ovarian cancer that is diagnosed is selected from the group consisting of serous ovarian cancer, mucinous ovarian cancer, endometrioid ovarian cancer and clear cell ovarian cancer.

44. A method of determining the likelihood of survival of a subject suffering from an ovarian cancer, said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein an elevated level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has a poor probability of survival, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

(i) a sequence comprising at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: NM_003014, AA046217, NM_015902, T83882, AB040888, AA628980, AI623351, AW614420, AA243499, AF251237, AI970797, AF145713, X78565, T97307, BE243845, AW068302, AL133561, BE313555, X07820, AI973016, AF084545, U41518, Z11894, AW138190, BE086548, W47196, AI796870, X02761, AW968613, AW972565, AF045229, AW953853, U52426, F06700, AI798863, H52761, BE546947, AU076643, U20536, AA581602, AJ245210, X65965, AI806770, BE386490, AW581992, U77534, AL034417, L10343, AW518944, W28729, AI640160, U11862, AW295980, X59135, BE466173, AI354722, M90464, AA829286, AI333771, BE465867, NM_014992,

BE616902, AA430373, R27430, BE387335, AW264102, AW952323, AA088177, BE614567, AL079658, NM_002776, BE261944, NM_006379, AI002238, X81789, NM_002122, AB001914, AA311919, AI381750, AA292998, BE439580, AI677897, N72403, BE003054, AL035588, AI080491, AW770994, H24177, AF146761, NM_001955, AI680737, AI752666, AA505445, BE246649, and NM_003955;

(ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: NM_003014, AA046217, NM_015902, T83882, AB040888, AA628980, AI623351, AW614420, AA243499, AF251237, AI970797, AF145713, X78565, T97307, BE243845, AW068302, AL133561, BE313555, X07820, AI973016, AF084545, U41518, Z11894, AW138190, BE086548, W47196, AI796870, X02761, AW968613, AW972565, AF045229, AW953853, U52426, F06700, AI798863, H52761, BE546947, AU076643, U20536, AA581602, AJ245210, X65965, AI806770, BE386490, AW581992, U77534, AL034417, L10343, AW518944, W28729, AI640160, U11862, AW295980, X59135, BE466173, AI354722, M90464, AA829286, AI333771, BE465867, NM_014992, BE616902, AA430373, R27430, BE387335, AW264102, AW952323, AA088177, BE614567, AL079658, NM_002776, BE261944, NM_006379, AI002238, X81789, NM_002122, AB001914, AA311919, AI381750, AA292998, BE439580, AI677897, N72403, BE003054, AL035588, AI080491, AW770994, H24177, AF146761, NM_001955, AI680737, AI752666, AA505445, BE246649, and NM_003955;

(iii) a sequence that is at least about 80% identical to (i) or (ii);

(iv) a sequence that encodes a polypeptide encoded by a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: NM_003014, AA046217, NM_015902, T83882, AB040888, AA628980, AI623351, AW614420, AA243499, AF251237, AI970797, AF145713, X78565, T97307, BE243845, AW068302, AL133561, BE313555, X07820, AI973016, AF084545, U41518, Z11894, AW138190, BE086548, W47196, AI796870, X02761, AW968613, AW972565, AF045229, AW953853, U52426, F06700, AI798863, H52761, BE546947, AU076643, U20536, AA581602, AJ245210, X65965, AI806770, BE386490, AW581992, U77534, AL034417, L10343, AW518944, W28729, AI640160, U11862, AW295980, X59135, BE466173, AI354722, M90464, AA829286, AI333771, BE465867, NM_014992, BE616902, AA430373, R27430, BE387335, AW264102, AW952323, AA088177, BE614567, AL079658, NM_002776, BE261944, NM_006379, AI002238, X81789, NM_002122,

AB001914, AA311919, AI381750, AA292998, BE439580, AI677897, N72403, BE003054, AL035588, AI080491, AW770994, H24177, AF146761, NM_001955, AI680737, AI752666, AA505445, BE246649, and NM_003955; and

(v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

45. The method of claim 44 wherein the nucleic acid probe comprises a sequence selected from the group consisting of:

(i) a sequence comprising at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 63, 65, 67, 69, 71, and 73;

(ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;

(iii) a sequence that is at least about 80% identical to a sequence selected from the group consisting of SEQ ID NOs: 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;

(iv) a sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NOs: 64, 66, 68, 70, 72, 74, 76, 78, 80, 82 and 84; and

(v) a sequence that is complementary to (i) or (ii) or (iii) or (iv).

46. A method of determining the likelihood of survival of a subject suffering from an ovarian cancer, said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein an enhanced level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer indicates that the subject being tested has has a poor probability of survival, and wherein said antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a sequence encoded by a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: NM_003014, AA046217, NM_015902, T83882, AB040888, AA628980, AI623351, AW614420, AA243499, AF251237, AI970797, AF145713, X78565, T97307, BE243845, AW068302, AL133561, BE313555, X07820, AI973016, AF084545, U41518, Z11894, AW138190, BE086548, W47196, AI796870, X02761, AW968613, AW972565, AF045229, AW953853, U52426, F06700, AI798863, H52761, BE546947, AU076643, U20536, AA581602, AJ245210, X65965, AI806770, BE386490, AW581992, U77534, AL034417, L10343, AW518944, W28729, AI640160, U11862, AW295980, X59135,

BE466173, AI354722, M90464, AA829286, AI333771, BE465867, NM_014992, BE616902, AA430373, R27430, BE387335, AW264102, AW952323, AA088177, BE614567, AL079658, NM_002776, BE261944, NM_006379, AI002238, X81789, NM_002122, AB001914, AA311919, AI381750, AA292998, BE439580, AI677897, N72403, BE003054, AL035588, AI080491, AW770994, H24177, AF146761, NM_001955, AI680737, AI752666, AA505445, BE246649, and NM_003955.

47. The method of claim 46 wherein the antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a sequence having at least about 80% identity to a sequence selected from the group consisting of SEQ ID NOs: 64, 66, 68, 70, 72, 74, 76, 78, 80, 82 and 84.

48. A method of determining the likelihood of survival of a subject suffering from a serous ovarian cancer, said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein an elevated level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has a poor probability of survival, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

(i) a sequence comprising at least about 20 contiguous nucleotides from a nucleic acid comprising the nucleotide sequence set forth in SEQ ID NO: 71 or 73;

(ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a nucleic acid comprising the nucleotide sequence set forth in SEQ ID NO: 71 or 73;

(iii) a sequence that is at least about 80% identical to (i) or (ii) and encoding an sFRP protein or a SOCS3 protein;

(iv) a sequence that encodes a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 72 or 74; and

(v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

49. A method of determining the likelihood of survival of a subject suffering from a serous ovarian cancer, said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein an enhanced

level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer indicates that the subject being tested has a poor probability of survival, and wherein said antibody binds to an sFRP polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 72 or a SOCS3 polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 74.

50. A method of determining the likelihood of survival of a subject suffering from a serous ovarian cancer, said method comprising contacting a biological sample from said subject being tested with at least two antibodies for a time and under conditions sufficient for antigen-antibody complexes to form and then detecting the complexes wherein an enhanced level of the antigen-antibody complexes for the subject being tested compared to the amount of the antigen-antibody complexes formed for a control subject not having ovarian cancer indicates that the subject being tested has a poor probability of survival, and wherein one antibody binds to an sFRP polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 72 and wherein one antibody binds to a SOCS3 polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 74.

51. The method according to any one of claims 44 to 47 wherein the ovarian cancer is an epithelial ovarian cancer.

52. The method according to any one of claims 44 to 47 wherein the ovarian cancer is selected from the group consisting of serous ovarian cancer, non-invasive ovarian cancer, mixed phenotype ovarian cancer, mucinous ovarian cancer, endometrioid ovarian cancer, clear cell ovarian cancer, papillary serous ovarian cancer, Brenner cell and undifferentiated adenocarcinoma.

53. The method according to claim 52 wherein the ovarian cancer is selected from the group consisting of serous ovarian cancer, mucinous ovarian cancer, endometrioid ovarian cancer and clear cell ovarian cancer.

54. A method of determining the likelihood that a subject will suffer from a recurrence of an ovarian cancer, said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein an elevated level of hybridization of the probe for the subject being tested compared to the hybridization

obtained for a control subject not having ovarian cancer indicates that the subject being tested has a high probability of recurrence, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

(i) a sequence comprising at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: M86849, AW963419, BE298665, AK000637, BE077546, T97307, R24601, BE090176, AA393907, W28729, BE313754, AW673081, AA356694, L08239, BE397649, NM_012317, NM_000947, AJ250562, AL040183, BE207573, BE564162, BE439580, AW067800, AA569756, AW138190, AF126245, L10343, NM_002514, AI863735, NM_005397, W26391, H15474, U51166, AA243499, AW408807, AI738719, AB040888, BE313077, AI677897, C14898, AI821730, AF007393, H65423, N46243, AA095971, U20350, NM_005756, D19589, AW957446, AW294647, BE159718, AI888490, AA022569, BE147740, AI798863, BE464341, AL080235, AI557212, X75208, AA628980, BE242587, NM_005512, AW953853, AU076611, AW968613, AL353944, BE614149, AA292998, H12912, AA188763, AK000596, AI970797, AW519204, Z42387, AF145713, AA972412, AK001564, AW959861, BE313555, W25005, AI193356, AF111106, AI130740, AA985190, BE221880, AF084545, R26584, AW247380, AA364261, U25849, AF262992, AW342140, AL133572, AI497778, AI745379, U51712, AW375974, AF251237, NM_000636, AA130986, AA216363, AA628980, AA811657, AA897108, AB040888, AF212225, AI089575, AI282028, AI368826, AI718702, AI827248, AK002039, AL109791, AW090198, AW296454, AW445034, AW452948, AW470411, AW885727, AW970859, AW979189, BE165866, BE175582, BE242587, BE271927, BE439580, BE464016, D63216, F34856, M83822, N33937, N49068, N51357, N80486, NM_000954, NM_005756, NM_016652, R26584, R31178, W05391, W25005, W45393, W68815, X65965, X76732 and Z45051,

(ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: M86849, AW963419, BE298665, AK000637, BE077546, T97307, R24601, BE090176, AA393907, W28729, BE313754, AW673081, AA356694, L08239, BE397649, NM_012317, NM_000947, AJ250562, AL040183, BE207573, BE564162, BE439580, AW067800, AA569756, AW138190, AF126245, L10343, NM_002514, AI863735, NM_005397, W26391, H15474, U51166, AA243499, AW408807, AI738719, AB040888, BE313077, AI677897, C14898, AI821730, AF007393,

H65423, N46243, AA095971, U20350, NM_005756, D19589, AW957446, AW294647, BE159718, AI888490, AA022569, BE147740, AI798863, BE464341, AL080235, AI557212, X75208, AA628980, BE242587, NM_005512, AW953853, AU076611, AW968613, AL353944, BE614149, AA292998, H12912, AA188763, AK000596, AI970797, AW519204, Z42387, AF145713, AA972412, AK001564, AW959861, BE313555, W25005, AI193356, AF111106, AI130740, AA985190, BE221880, AF084545, R26584, AW247380, AA364261, U25849, AF262992, AW342140, AL133572, AI497778, AI745379, U51712, AW375974, AF251237, NM_000636, AA130986, AA216363, AA628980, AA811657, AA897108, AB040888, AF212225, AI089575, AI282028, AI368826, AI718702, AI827248, AK002039, AL109791, AW090198, AW296454, AW445034, AW452948, AW470411, AW885727, AW970859, AW979189, BE165866, BE175582, BE242587, BE271927, BE439580, BE464016, D63216, F34856, M83822, N33937, N49068, N51357, N80486, NM_000954, NM_005756, NM_016652, R26584, R31178, W05391, W25005, W45393, W68815, X65965, X76732 and Z45051;

(iii) a sequence that is at least about 80% identical to (i) or (ii);

(iv) a sequence that encodes a polypeptide encoded by a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of:M86849, AW963419, BE298665, AK000637, BE077546, T97307, R24601, BE090176, AA393907, W28729, BE313754, AW673081, AA356694, L08239, BE397649, NM_012317, NM_000947, AJ250562, AL040183, BE207573, BE564162, BE439580, AW067800, AA569756, AW138190, AF126245, L10343, NM_002514, AI863735, NM_005397, W26391, H15474, U51166, AA243499, AW408807, AI738719, AB040888, BE313077, AI677897, C14898, AI821730, AF007393, H65423, N46243, AA095971, U20350, NM_005756, D19589, AW957446, AW294647, BE159718, AI888490, AA022569, BE147740, AI798863, BE464341, AL080235, AI557212, X75208, AA628980, BE242587, NM_005512, AW953853, AU076611, AW968613, AL353944, BE614149, AA292998, H12912, AA188763, AK000596, AI970797, AW519204, Z42387, AF145713, AA972412, AK001564, AW959861, BE313555, W25005, AI193356, AF111106, AI130740, AA985190, BE221880, AF084545, R26584, AW247380, AA364261, U25849, AF262992, AW342140, AL133572, AI497778, AI745379, U51712, AW375974, AF251237, NM_000636, AA130986, AA216363, AA628980, AA811657, AA897108, AB040888, AF212225, AI089575, AI282028, AI368826, AI718702, AI827248, AK002039, AL109791, AW090198, AW296454, AW445034,

AW452948, AW470411, AW885727, AW970859, AW979189, BE165866, BE175582, BE242587, BE271927, BE439580, BE464016, D63216, F34856, M83822, N33937, N49068, N51357, N80486, NM_000954, NM_005756, NM_016652, R26584, R31178, W05391, W25005, W45393, W68815, X65965, X76732 and Z45051; and

(v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

55. The method of claim 54 determining the likelihood that a subject will suffer from a recurrence of an ovarian cancer, said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein an enhanced level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer indicates that the subject being tested has a high probability of recurrence, and wherein said antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a sequence encoded by a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: M86849, AW963419, BE298665, AK000637, BE077546, T97307, R24601, BE090176, AA393907, W28729, BE313754, AW673081, AA356694, L08239, BE397649, NM_012317, NM_000947, AJ250562, AL040183, BE207573, BE564162, BE439580, AW067800, AA569756, AW138190, AF126245, L10343, NM_002514, AI863735, NM_005397, W26391, H15474, U51166, AA243499, AW408807, AI738719, AB040888, BE313077, AI677897, C14898, AI821730, AF007393, H65423, N46243, AA095971, U20350, NM_005756, D19589, AW957446, AW294647, BE159718, AI888490, AA022569, BE147740, AI798863, BE464341, AL080235, AI557212, X75208, AA628980, BE242587, NM_005512, AW953853, AU076611, AW968613, AL353944, BE614149, AA292998, H12912, AA188763, AK000596, AI970797, AW519204, Z42387, AF145713, AA972412, AK001564, AW959861, BE313555, W25005, AI193356, AF111106, AI130740, AA985190, BE221880, AF084545, R26584, AW247380, AA364261, U25849, AF262992, AW342140, AL133572, AI497778, AI745379, U51712, AW375974, AF251237, NM_000636, AA130986, AA216363, AA628980, AA811657, AA897108, AB040888, AF212225, AI089575, AI282028, AI368826, AI718702, AI827248, AK002039, AL109791, AW090198, AW296454, AW445034, AW452948, AW470411, AW885727, AW970859, AW979189, BE165866, BE175582, BE242587, BE271927, BE439580,

BE464016, D63216, F34856, M83822, N33937, N49068, N51357, N80486, NM_000954, NM_005756, NM_016652, R26584, R31178, W05391, W25005, W45393, W68815, X65965, X76732 and Z45051.

56. The method according to claim 54 or 55 wherein the ovarian cancer is an epithelial ovarian cancer.

57. The method according to any one of claims 54 to 56 wherein the ovarian cancer is selected from the group consisting of serous ovarian cancer, non-invasive ovarian cancer, mixed phenotype ovarian cancer, mucinous ovarian cancer, endometrioid ovarian cancer, clear cell ovarian cancer, papillary serous ovarian cancer, Brenner cell and undifferentiated adenocarcinoma.

58. The method according to claim 57 wherein the ovarian cancer is selected from the group consisting of serous ovarian cancer, mucinous ovarian cancer, endometrioid ovarian cancer and clear cell ovarian cancer.

59. The method according to any one of claims 35 to 58 wherein the biological sample is contacted with a plurality of nucleic acid probes and/or antibodies and/or polypeptides.

60. A method for identifying a compound that modulates an ovarian cancer-associated polypeptide, the method comprising :

(i) contacting the compound with a ovarian cancer-associated polypeptide, the polypeptide encoded by a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-3; and

(ii) determining the functional effect of the compound upon the polypeptide.

61. A method for determining a candidate compound for the treatment of ovarian cancer comprising :

(i) administering a test compound to a mammal having ovarian cancer or a cell isolated therefrom;

(ii) comparing the level of gene expression of a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-3 in a treated cell or mammal with the level of gene expression of the polynucleotide in a control cell or mammal, wherein a test compound that

modulates the level of expression of the polynucleotide is a candidate for the treatment of ovarian cancer.

62. An assay device for use in the diagnosis or prognosis of ovarian cancer, said device comprising a plurality of polynucleotides immobilized to a solid phase, wherein each of said polnucleotides consists of a gene as listed in any one of Tables 1-3.

63. The device of claim 62 consisting of a substantially planar chip.

64. An assay device for use in the diagnosis or prognosis of ovarian cancer, said device comprising a plurality of different antibodies immobilized to a solid phase, wherein each of said antibodies binds to a polypeptide listed in Tables 1-3.

65. The device of claim 64 consisting of a substantially planar chip.

66. Use of a polynucleotide as set forth in any one of Tables 1-3 in the diagnosis or prognosis of ovarian cancer or for the preparation of a medicament for the treatment of ovarian cancer.

67. Use of a vector comprising a polynucleotide as set forth in any one of Tables 1-3 in the diagnosis or prognosis of ovarian cancer or for the preparation of a medicament for the treatment of ovarian cancer.

68. Use of an isolated polypeptide as set forth in any one of Tables 1-3 in the diagnosis or prognosis of ovarian cancer or for the preparation of a medicament for the treatment of ovarian cancer.

69. Use of an antibody that binds to an isolated polypeptide as set forth in any one of Tables 1-3 in the diagnosis or prognosis of ovarian cancer or for the preparation of a medicament for the treatment of ovarian cancer.

70. A method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising determining aberrant methylation in a promoter sequence that regulates expression of a tumor suppressor gene in a biological sample from said subject compared to the methylation of the promoter in nucleic acid obtained for a control

subject not having ovarian cancer wherein said aberrant methylation indicates that the subject being tested has an ovarian ovarian cancer.

71. The method of claim 70 wherein hypermethylation of the promoter sequence is determined.

72. The method of claim 70 or 71 wherein the methylation is determined in the promoter region that regulates expression of an MCC gene comprising a sequence selected from the group consisting of:

(i) the nucleotide sequence set forth as SEQ ID NO: 3;

(ii) a sequence that hybridizes under at least low stringency hybridization conditions to the nucleotide sequence set forth as SEQ ID NO: 3;

(iii) a sequence that is at least about 80% identical to (i) or (ii);

(iv) a sequence that encodes a polypeptide encoded by a nucleotide sequence set forth as SEQ ID NO: 3; and

(v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

73. The method according to any one of claims 70 to 72 wherein the ovarian cancer that is diagnosed is an epithelial ovarian cancer.

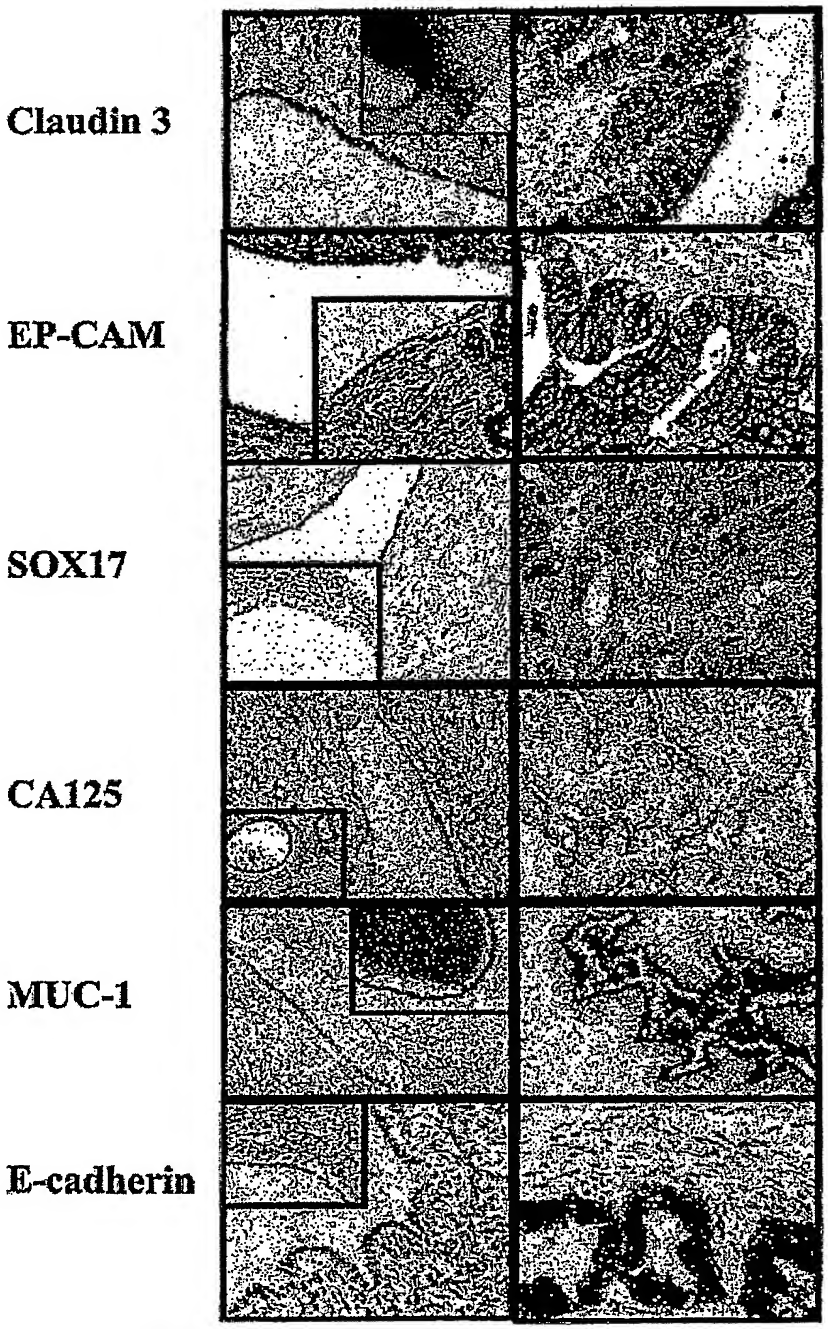
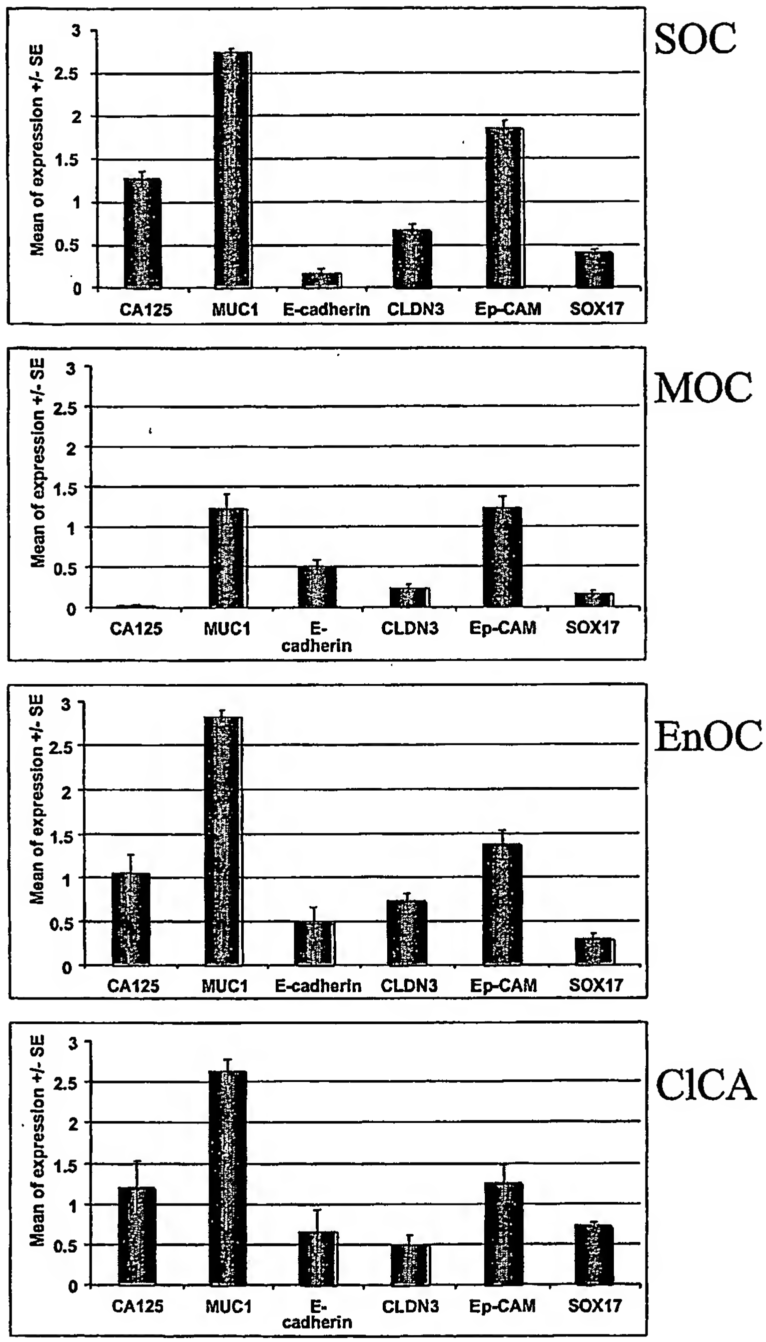


FIGURE 1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MOC
EnOC
ClCA
Mean of expression +/- SE
3
2.5
2
1.5
1
0.5
0
CA125
MUC1
E-cadherin
CLDN3
Ep-CAM
SOX17

FIGURE 2

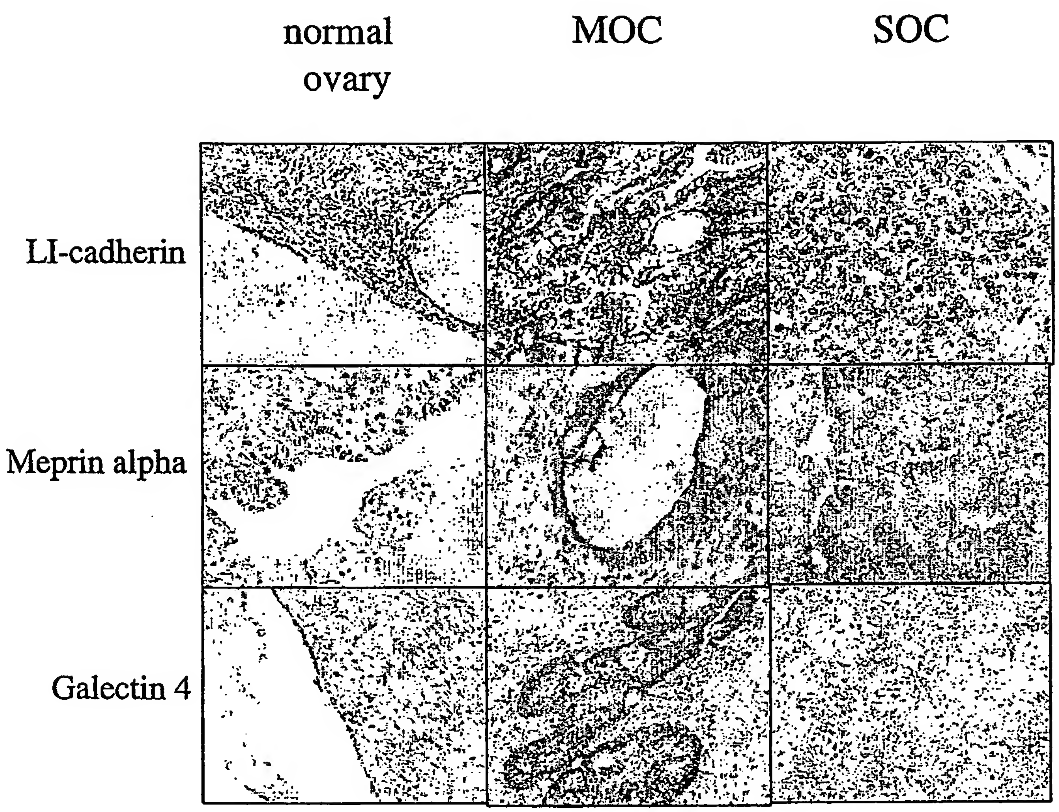


FIGURE 3

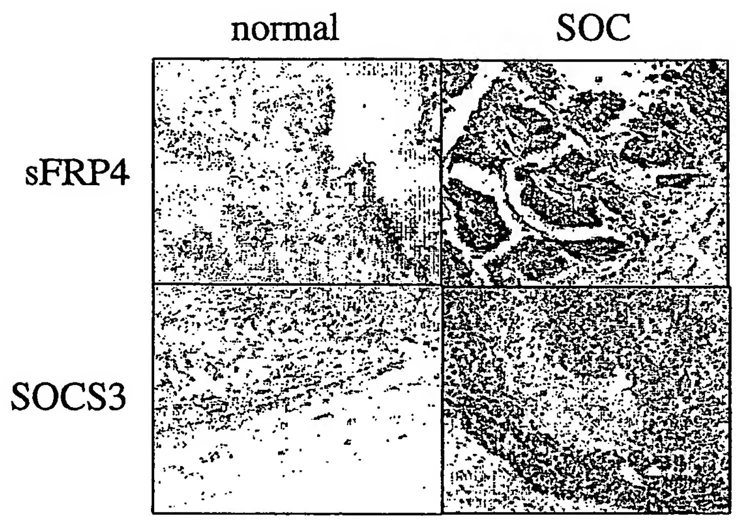
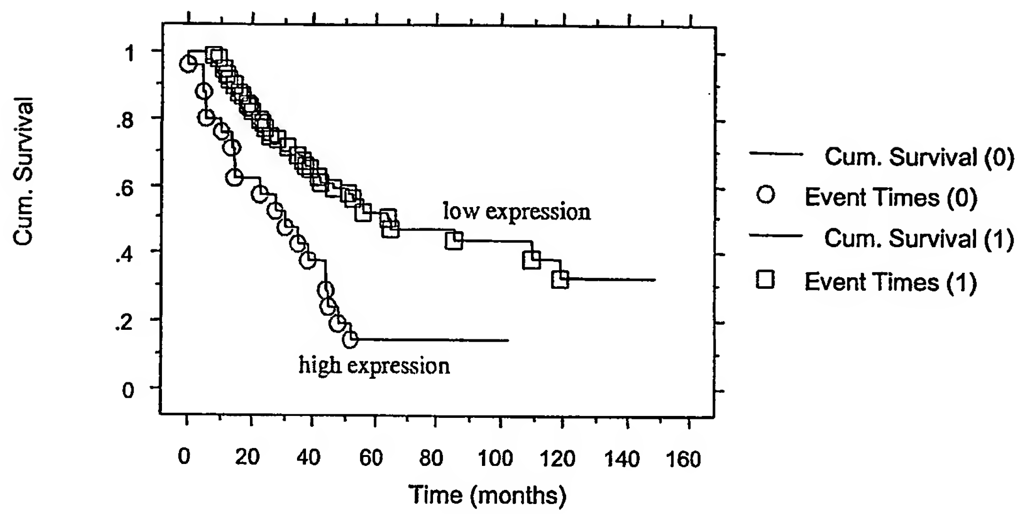


FIGURE 4a



Cum. Survival
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.8
.6
.4
.2
0
low expression
high expression
0
20
40
60
80
100
120
140
160
Time (months)
Cum. Survival (0)
Event Times (0)
Cum. Survival (1)
Event Times (1)

FIGURE 4b

SEQUENCE LISTING

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<120>  Methods for the diagnosis and prognosis of ovarian cancer

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<151>  2002-09-05

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<170>  PatentIn version 3.1

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                                     Met Glu Ala Pro Glu Tyr Leu
                                     1               5

gat ttg gat gaa att gac ttt agt gat gac ata tct tat tca gtc aca      162
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        10                  15                  20

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Ser Leu Lys Thr Ile Pro Glu Leu Cys Arg Arg Cys Asp Thr Gln Asn
    25                  30                  35

gaa gac aga tca gct tct agc tct agc tgg aat tgt ggc atc tca act      258
Glu Asp Arg Ser Ala Ser Ser Ser Ser Trp Asn Cys Gly Ile Ser Thr
40                  45                  50                  55

ctt att aca aac acg caa aag ccc aca gga atc gct gat gtg tac agt      306
Leu Ile Thr Asn Thr Gln Lys Pro Thr Gly Ile Ala Asp Val Tyr Ser
                60                  65                  70

aag ttc cgc cca gtg aag cgg gtt tcg cca ctg aaa cat cag cca gag      354
Lys Phe Arg Pro Val Lys Arg Val Ser Pro Leu Lys His Gln Pro Glu
            75                  80                  85

act ctg gag aac aat gaa agt gat gac caa aag aac cag aaa gtg gtt      402
Thr Leu Glu Asn Asn Glu Ser Asp Asp Gln Lys Asn Gln Lys Val Val
        90                  95                  100

gag tac cag aaa ggg ggt gag tct gac ctg ggc ccc cag cct cag gag      450
Glu Tyr Gln Lys Gly Gly Glu Ser Asp Leu Gly Pro Gln Pro Gln Glu
    105                 110                 115

ctt ggc cct gga gat gga gtg ggc ggc cca cca ggt aag agc tct gag      498
Leu Gly Pro Gly Asp Gly Val Gly Gly Pro Pro Gly Lys Ser Ser Glu
120                 125                 130                 135

ccc agc aca tcg ctg ggt gaa ctg gag cac tac gac ctc gac atg gat      546
Pro Ser Thr Ser Leu Gly Glu Leu Glu His Tyr Asp Leu Asp Met Asp
                140                 145                 150
```

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ttt acc aag gtg act tca gaa aaa aga att ttg ggc tta tgc aca acc      642
Phe Thr Lys Val Thr Ser Glu Lys Arg Ile Leu Gly Leu Cys Thr Thr
        170                 175                 180

atc aat ggc ctt tct ggc aaa gcc tgc tct aca gga agt tct gag agc      690
Ile Asn Gly Leu Ser Gly Lys Ala Cys Ser Thr Gly Ser Ser Glu Ser
    185                 190                 195

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200                 205                 210                 215

cct cac ttg aga aaa gca tca gct gtc atc cac gac cag cac aag ctg      786
Pro His Leu Arg Lys Ala Ser Ala Val Ile His Asp Gln His Lys Leu
                220                 225                 230

tcc act gaa gaa acc gag atc tca cct cct ctg gtt aaa tgt ggc tct      834
Ser Thr Glu Glu Thr Glu Ile Ser Pro Pro Leu Val Lys Cys Gly Ser
            235                 240                 245

gca tat gag cct gaa aac cag agt aaa gac ttc cta aac aag aca ttt      882
Ala Tyr Glu Pro Glu Asn Gln Ser Lys Asp Phe Leu Asn Lys Thr Phe
        250                 255                 260

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    265                 270                 275

ctc agg gcc ttc cac cta caa tcc tca gca gca gaa tcc aaa cca gaa      978
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280                 285                 290                 295

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agg agt gag tat ctg aaa aaa gtg aaa agc atc ttg aac att gtt aaa     1074
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gaa gga cag atc tct ctc ctg cca cac cta gct gca gac aat cta gac     1122
Glu Gly Gln Ile Ser Leu Leu Pro His Leu Ala Ala Asp Asn Leu Asp
        330                 335                 340

aaa att cac gac gaa aat gga aac aat cta tta cat att gcg gcg tca     1170
Lys Ile His Asp Glu Asn Gly Asn Asn Leu Leu His Ile Ala Ala Ser
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cag gga cac gca gag tgt cta cag cac ctc act tct ttg atg gga gaa     1218
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360                 365                 370                 375

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Gly Ile Ala Asp Val Tyr Ser Lys Phe Arg Pro Val Lys Arg Val Ser
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Lys Leu Thr Pro Ala Gly Leu Ala Ile Lys Asn Gly Gln Leu Glu Cys
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Ser Lys Asp Phe Pro Ser Leu Ile His Tyr Ala Gly Cys Tyr Gly Gln
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Glu Lys Ile Leu Leu Trp Leu Leu Gln Phe Met Gln Glu Gln Gly Ile
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Ser Leu Asp Glu Val Asp Gln Asp Gly Asn Ser Ala Val His Val Ala
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Glu Thr Cys Met Ser Leu Ala Ser Gln Val Val Lys Leu Thr Lys Gln
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    530                 535                 540

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Glu Phe Gln Asp Ala Gln Ala Ser Ser Arg Asn Ser Lys Lys Ile Pro
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Leu Glu Lys Arg Glu Leu Lys Leu Ala Arg Leu Arg Gln Leu Met Gln
            660                 665                 670

Arg Ser Leu Ser Glu Ser Asp Thr Asp Ser Asn Asn Ser Glu Asp Pro
        675                 680                 685

Lys Thr Thr Pro Val Arg Lys Ala Asp Arg Pro Arg Pro Gln Pro Ile
    690                 695                 700

Val Glu Ser Val Glu Ser Met Asp Ser Ala Glu Ser Leu His Leu Met
705                 710                 715                 720

Ile Lys Lys His Thr Leu Ala Ser Gly Gly Arg Arg Phe Pro Phe Ser
                725                 730                 735
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Ile Lys Ala Ser Lys Ser Leu Asp Gly His Ser Pro Ser Pro Thr Ser
740 745 750

Glu Ser Ser Glu Pro Asp Leu Glu Ser Gln Tyr Pro Gly Ser Gly Ser
755 760 765

Ile Pro Pro Asn Gln Pro Ser Gly Asp Pro Gln Gln Pro Ser Pro Asp
770 775 780

Ser Thr Ala Ala Gln Lys Val Ala Thr Ser Pro Lys Ser Ala Leu Lys
785 790 795 800

Ser Pro Ser Ser Lys Arg Arg Thr Ser Gln Asn Leu Lys Leu Arg Val
805 810 815

Thr Phe Glu Glu Pro Val Val Gln Met Glu Gln Pro Ser Leu Glu Leu
820 825 830

Asn Gly Glu Lys Asp Lys Asp Lys Gly Arg Thr Leu Gln Arg Thr Ser
835 840 845

Thr Ser Asn Glu Ser Gly Asp Gln Leu Lys Arg Pro Phe Gly Ala Phe
850 855 860

Arg Ser Ile Met Glu Thr Leu Ser Gly Asn Gln Asn Asn Asn Asn Asn
865 870 875 880

Tyr Gln Ala Ala Asn Gln Leu Lys Thr Ser Thr Leu Pro Leu Thr Ser
885 890 895

Leu Gly Arg Lys Thr Asp Ala Lys Gly Asn Pro Ala Ser Ser Ala Ser
900 905 910

Lys Gly Lys Asn Lys Ala Ala
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tgtggcagaa gggaccaagc agtggatatt gagcctgtga agtccaactc ttaagctccg 180

agacctgggg gactgagagc ccagctctga aaagtgcatc atg aat tcc gga gtt 235
Met Asn Ser Gly Val
1 5

gcc atg aaa tat gga aac gac tcc tcg gcc gag ctg agt gag ctc cat 283
Ala Met Lys Tyr Gly Asn Asp Ser Ser Ala Glu Leu Ser Glu Leu His
10 15 20

tca gca gcc ctg gca tca cta aag gga gat ata gtg gaa ctt aat aaa 331
Ser Ala Ala Leu Ala Ser Leu Lys Gly Asp Ile Val Glu Leu Asn Lys
25 30 35

cgt ctc cag caa aca gag agg gaa cgg gac ctt ctg gaa aag aaa ttg 379
Arg Leu Gln Gln Thr Glu Arg Glu Arg Asp Leu Leu Glu Lys Lys Leu
40 45 50

gcc aag gca cag tgc gag cag tcc cac ctc atg aga gag cat gag gat 427
Ala Lys Ala Gln Cys Glu Gln Ser His Leu Met Arg Glu His Glu Asp
55 60 65

gtc cag gag cga acg acg ctt cgc tat gag gaa cgc atc aca gag ctc 475
Val Gln Glu Arg Thr Thr Leu Arg Tyr Glu Glu Arg Ile Thr Glu Leu
70 75 80 85

cac agc gtc att gcg gag ctc aac aag aag ata gac cgt ctg caa ggc 523
His Ser Val Ile Ala Glu Leu Asn Lys Lys Ile Asp Arg Leu Gln Gly
90 95 100

acc acc atc agg gag gaa gat gag tac tca gaa ctg cga tca gaa ctc 571
Thr Thr Ile Arg Glu Glu Asp Glu Tyr Ser Glu Leu Arg Ser Glu Leu
105 110 115

agc cag agc caa cac gag gtc aac gag gac tct cga agc atg gac caa 619
Ser Gln Ser Gln His Glu Val Asn Glu Asp Ser Arg Ser Met Asp Gln
120 125 130

gac cag acc tct gtc tct atc ccc gaa aac cag tct acc atg gtt act 667
Asp Gln Thr Ser Val Ser Ile Pro Glu Asn Gln Ser Thr Met Val Thr
135 140 145

gct gac atg gac aac tgc agt gac ctg aac tca gaa ctg cag agg gtg 715
Ala Asp Met Asp Asn Cys Ser Asp Leu Asn Ser Glu Leu Gln Arg Val
150 155 160 165

ctg aca ggg ctg gag aat gtt gtc tgc ggc agg aag aag agc agc tgc 763
Leu Thr Gly Leu Glu Asn Val Val Cys Gly Arg Lys Lys Ser Ser Cys
170 175 180

agc ctc tcc gtg gcc gag gtg gac agg cac att gag cag ctc acc aca 811
Ser Leu Ser Val Ala Glu Val Asp Arg His Ile Glu Gln Leu Thr Thr
185 190 195

gcc agc gag cac tgt gac ctg gct att aag aca gtc gag gag att gag 859
Ala Ser Glu His Cys Asp Leu Ala Ile Lys Thr Val Glu Glu Ile Glu
200 205 210

ggg gtg ctt ggc cgg gac ctg tat ccc aac ctg gct gaa gag agg tct 907
Gly Val Leu Gly Arg Asp Leu Tyr Pro Asn Leu Ala Glu Glu Arg Ser
215 220 225

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cgg tgg gag aag gag ctg gct ggg ctg agg gaa gag aat gag agc ctg        955
Arg Trp Glu Lys Glu Leu Ala Gly Leu Arg Glu Glu Asn Glu Ser Leu
230                 235                 240                 245

act gcc atg ctg tgc agc aaa gag gaa gaa ctg aac cgg act aag gcc       1003
Thr Ala Met Leu Cys Ser Lys Glu Glu Glu Leu Asn Arg Thr Lys Ala
                250                 255                 260

acc atg aat gcc atc cgg gaa gag cgg gac cgg ctc cgg agg cgg gtc       1051
Thr Met Asn Ala Ile Arg Glu Glu Arg Asp Arg Leu Arg Arg Arg Val
            265                 270                 275

aga gag ctt caa act cga cta cag agc gtg cag gcc aca ggt ccc tcc       1099
Arg Glu Leu Gln Thr Arg Leu Gln Ser Val Gln Ala Thr Gly Pro Ser
        280                 285                 290

agc cct ggc cgc ctc act tcc acc aac cgc ccg att aac ccc agc act       1147
Ser Pro Gly Arg Leu Thr Ser Thr Asn Arg Pro Ile Asn Pro Ser Thr
    295                 300                 305

ggg gag ctg agc aca agc agc agc agc aat gac att ccc atc gcc aag       1195
Gly Glu Leu Ser Thr Ser Ser Ser Ser Asn Asp Ile Pro Ile Ala Lys
310                 315                 320                 325

att gct gag agg gtg aag cta tca aag aca agg tcc gaa tcg tca tca       1243
Ile Ala Glu Arg Val Lys Leu Ser Lys Thr Arg Ser Glu Ser Ser Ser
                330                 335                 340

tct gat cgg cca gtc ctg ggc tca gaa atc agt agc ata ggg gta tcc       1291
Ser Asp Arg Pro Val Leu Gly Ser Glu Ile Ser Ser Ile Gly Val Ser
            345                 350                 355

agc agt gtg gct gaa cac ctg gcc cac tca ctt cag gac tgc tcc aat       1339
Ser Ser Val Ala Glu His Leu Ala His Ser Leu Gln Asp Cys Ser Asn
        360                 365                 370

atc caa gag att ttc caa aca ctc tac tca cac gga tct gcc atc tca       1387
Ile Gln Glu Ile Phe Gln Thr Leu Tyr Ser His Gly Ser Ala Ile Ser
    375                 380                 385

gaa agc aag att aga gag ttt gag gtg gaa aca gaa cgg ctg aat agc       1435
Glu Ser Lys Ile Arg Glu Phe Glu Val Glu Thr Glu Arg Leu Asn Ser
390                 395                 400                 405

cgg att gag cac ctc aaa tcc caa aat gac ctc ctg acc ata acc ttg       1483
Arg Ile Glu His Leu Lys Ser Gln Asn Asp Leu Leu Thr Ile Thr Leu
                410                 415                 420

gag gaa tgt aaa agc aat gct gag agg atg agc atg ctg gtg gga aaa       1531
Glu Glu Cys Lys Ser Asn Ala Glu Arg Met Ser Met Leu Val Gly Lys
            425                 430                 435

tac gaa tcc aat gcc aca gcg ctg agg ctg gcc ttg cag tac agc gag       1579
Tyr Glu Ser Asn Ala Thr Ala Leu Arg Leu Ala Leu Gln Tyr Ser Glu
        440                 445                 450

cag tgc atc gaa gcc tac gaa ctc ctc ctg gcg ctg gca gag agt gag       1627
Gln Cys Ile Glu Ala Tyr Glu Leu Leu Leu Ala Leu Ala Glu Ser Glu
    455                 460                 465

cag agc ctc atc ctg ggg cag ttc cga gcg gcg ggc gtg ggg tcc tcc       1675
Gln Ser Leu Ile Leu Gly Gln Phe Arg Ala Ala Gly Val Gly Ser Ser
470                 475                 480                 485

cct gga gac cag tcg ggg gat gaa aac atc act cag atg ctc aag cga       1723
Pro Gly Asp Gln Ser Gly Asp Glu Asn Ile Thr Gln Met Leu Lys Arg
                490                 495                 500
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gct cat gac tgc cgg aag aca gct gag aac gct gcc aag gcc ctg ctc      1771
Ala His Asp Cys Arg Lys Thr Ala Glu Asn Ala Ala Lys Ala Leu Leu
            505                 510                 515

atg aag ctg gac ggc agc tgt ggg gga gcc ttt gcc gtg gcc ggc tgc      1819
Met Lys Leu Asp Gly Ser Cys Gly Gly Ala Phe Ala Val Ala Gly Cys
        520                 525                 530

agc gtg cag ccc tgg gag agc ctt tcc tcc aac agc cac acc agc aca      1867
Ser Val Gln Pro Trp Glu Ser Leu Ser Ser Asn Ser His Thr Ser Thr
    535                 540                 545

acc agc tcc aca gcc agt agt tgc gac acc gag ttc act aaa gaa gac      1915
Thr Ser Ser Thr Ala Ser Ser Cys Asp Thr Glu Phe Thr Lys Glu Asp
550                 555                 560                 565

gag cag agg ctg aag gat tat atc cag cag ctc aag aat gac agg gct      1963
Glu Gln Arg Leu Lys Asp Tyr Ile Gln Gln Leu Lys Asn Asp Arg Ala
                570                 575                 580

gcg gtc aag ctg acc atg ctg gag ctg gaa agc atc cac atc gat cct      2011
Ala Val Lys Leu Thr Met Leu Glu Leu Glu Ser Ile His Ile Asp Pro
            585                 590                 595

ctc agc tat gac gtc aag cct cgg gga gac agc cag agg ctg gat ctg      2059
Leu Ser Tyr Asp Val Lys Pro Arg Gly Asp Ser Gln Arg Leu Asp Leu
        600                 605                 610

gaa aac gca gtg ctt atg cag gag ctc atg gcc atg aag gag gag atg      2107
Glu Asn Ala Val Leu Met Gln Glu Leu Met Ala Met Lys Glu Glu Met
    615                 620                 625

gcc gag ttg aag gcc cag ctc tac cta ctg gag aaa gag aag aag gcc      2155
Ala Glu Leu Lys Ala Gln Leu Tyr Leu Leu Glu Lys Glu Lys Lys Ala
630                 635                 640                 645

ctg gag ctg aag ctg agc acg cgg gag gcc cag gag cag gcc tac ctg      2203
Leu Glu Leu Lys Leu Ser Thr Arg Glu Ala Gln Glu Gln Ala Tyr Leu
                650                 655                 660

gtg cac att gag cac ctg aag tcc gag gtg gag gag cag aag gag cag      2251
Val His Ile Glu His Leu Lys Ser Glu Val Glu Glu Gln Lys Glu Gln
            665                 670                 675

cgg atg cga tcc ctc agc tcc acc agc agc ggc agc aaa gat aaa cct      2299
Arg Met Arg Ser Leu Ser Ser Thr Ser Ser Gly Ser Lys Asp Lys Pro
        680                 685                 690

ggc aag gag tgt gct gat gct gcc tcc cca gct ctg tcc cta gct gaa      2347
Gly Lys Glu Cys Ala Asp Ala Ala Ser Pro Ala Leu Ser Leu Ala Glu
    695                 700                 705

ctc agg aca acg tgc agc gag aat gag ctg gct gcg gag ttc acc aac      2395
Leu Arg Thr Thr Cys Ser Glu Asn Glu Leu Ala Ala Glu Phe Thr Asn
710                 715                 720                 725

gcc att cgt cga gaa aag aag ttg aag gcc aga gtt caa gag ctg gtg      2443
Ala Ile Arg Arg Glu Lys Lys Leu Lys Ala Arg Val Gln Glu Leu Val
                730                 735                 740

agt gcc ttg gag aga ctc acc aag agc agt gaa atc cga cat cag caa      2491
Ser Ala Leu Glu Arg Leu Thr Lys Ser Ser Glu Ile Arg His Gln Gln
            745                 750                 755

tct gca gag ttc gtg aat gat cta aag cgg gcc aac agc aac ctg gtg      2539
Ser Ala Glu Phe Val Asn Asp Leu Lys Arg Ala Asn Ser Asn Leu Val
        760                 765                 770
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gct gcc tat gag aaa gca aag aaa aag cat caa aac aaa ctg aag aag 2587
Ala Ala Tyr Glu Lys Ala Lys Lys Lys His Gln Asn Lys Leu Lys Lys
775 780 785

tta gag tcg cag atg atg gcc atg gtg gag aga cat gag acc caa gtg 2635
Leu Glu Ser Gln Met Met Ala Met Val Glu Arg His Glu Thr Gln Val
790 795 800 805

agg atg ctc aag caa aga ata gct ctg cta gag gag gag aac tcc agg 2683
Arg Met Leu Lys Gln Arg Ile Ala Leu Leu Glu Glu Glu Asn Ser Arg
810 815 820

cca cac acc aat gaa act tcg ctt taatcagcac tcacgcaccg gagttctgcc 2737
Pro His Thr Asn Glu Thr Ser Leu
825

catgggaagt aaactgcagc aggccactgg ggacagaagg gcccatgtac ttgttgggag 2797

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aacccttggg gtgactggcc atggtgacat tgtggactgt atccagaggt gcccgctctt 2917

ccctcctggg cccacaacag cgtgtaaaca catgttctgt gcctgctcag cagagcctcg 2977

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ctgtagtgga actaaaattc tgtcaggggt ttcttcaaga gctgagaaac attattagca 3577

cttcccgccc cagggcacta cataattgct gttctgctga atcaaatctc ttccacatgg 3637

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<213> NM_002387 MCC, mutated in colorectal cancers

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Val Glu Leu Asn Lys Arg Leu Gln Gln Thr Glu Arg Glu Arg Asp Leu
        35   40   45

Leu Glu Lys Lys Leu Ala Lys Ala Gln Cys Glu Gln Ser His Leu Met
    50   55   60

Arg Glu His Glu Asp Val Gln Glu Arg Thr Thr Leu Arg Tyr Glu Glu
65   70   75   80

Arg Ile Thr Glu Leu His Ser Val Ile Ala Glu Leu Asn Lys Lys Ile
                85   90   95

Asp Arg Leu Gln Gly Thr Thr Ile Arg Glu Glu Asp Glu Tyr Ser Glu
            100   105   110

Leu Arg Ser Glu Leu Ser Gln Ser Gln His Glu Val Asn Glu Asp Ser
        115   120   125

Arg Ser Met Asp Gln Asp Gln Thr Ser Val Ser Ile Pro Glu Asn Gln
    130   135   140

Ser Thr Met Val Thr Ala Asp Met Asp Asn Cys Ser Asp Leu Asn Ser
145   150   155   160

Glu Leu Gln Arg Val Leu Thr Gly Leu Glu Asn Val Val Cys Gly Arg
                165   170   175

Lys Lys Ser Ser Cys Ser Leu Ser Val Ala Glu Val Asp Arg His Ile
            180   185   190

Glu Gln Leu Thr Thr Ala Ser Glu His Cys Asp Leu Ala Ile Lys Thr
        195   200   205

Val Glu Glu Ile Glu Gly Val Leu Gly Arg Asp Leu Tyr Pro Asn Leu
    210   215   220

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Ala Glu Glu Arg Ser Arg Trp Glu Lys Glu Leu Ala Gly Leu Arg Glu
225                 230                 235                 240

Glu Asn Glu Ser Leu Thr Ala Met Leu Cys Ser Lys Glu Glu Glu Leu
                245                 250                 255

Asn Arg Thr Lys Ala Thr Met Asn Ala Ile Arg Glu Glu Arg Asp Arg
            260                 265                 270

Leu Arg Arg Arg Val Arg Glu Leu Gln Thr Arg Leu Gln Ser Val Gln
        275                 280                 285

Ala Thr Gly Pro Ser Ser Pro Gly Arg Leu Thr Ser Thr Asn Arg Pro
    290                 295                 300

Ile Asn Pro Ser Thr Gly Glu Leu Ser Thr Ser Ser Ser Ser Asn Asp
305                 310                 315                 320

Ile Pro Ile Ala Lys Ile Ala Glu Arg Val Lys Leu Ser Lys Thr Arg
                325                 330                 335

Ser Glu Ser Ser Ser Ser Asp Arg Pro Val Leu Gly Ser Glu Ile Ser
            340                 345                 350

Ser Ile Gly Val Ser Ser Ser Val Ala Glu His Leu Ala His Ser Leu
        355                 360                 365

Gln Asp Cys Ser Asn Ile Gln Glu Ile Phe Gln Thr Leu Tyr Ser His
    370                 375                 380

Gly Ser Ala Ile Ser Glu Ser Lys Ile Arg Glu Phe Glu Val Glu Thr
385                 390                 395                 400

Glu Arg Leu Asn Ser Arg Ile Glu His Leu Lys Ser Gln Asn Asp Leu
                405                 410                 415

Leu Thr Ile Thr Leu Glu Glu Cys Lys Ser Asn Ala Glu Arg Met Ser
            420                 425                 430

Met Leu Val Gly Lys Tyr Glu Ser Asn Ala Thr Ala Leu Arg Leu Ala
        435                 440                 445

Leu Gln Tyr Ser Glu Gln Cys Ile Glu Ala Tyr Glu Leu Leu Leu Ala
    450                 455                 460

Leu Ala Glu Ser Glu Gln Ser Leu Ile Leu Gly Gln Phe Arg Ala Ala
465                 470                 475                 480

Gly Val Gly Ser Ser Pro Gly Asp Gln Ser Gly Asp Glu Asn Ile Thr
                485                 490                 495
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Gln Met Leu Lys Arg Ala His Asp Cys Arg Lys Thr Ala Glu Asn Ala
500 505 510

Ala Lys Ala Leu Leu Met Lys Leu Asp Gly Ser Cys Gly Gly Ala Phe
515 520 525

Ala Val Ala Gly Cys Ser Val Gln Pro Trp Glu Ser Leu Ser Ser Asn
530 535 540

Ser His Thr Ser Thr Thr Ser Ser Thr Ala Ser Ser Cys Asp Thr Glu
545 550 555 560

Phe Thr Lys Glu Asp Glu Gln Arg Leu Lys Asp Tyr Ile Gln Gln Leu
565 570 575

Lys Asn Asp Arg Ala Ala Val Lys Leu Thr Met Leu Glu Leu Glu Ser
580 585 590

Ile His Ile Asp Pro Leu Ser Tyr Asp Val Lys Pro Arg Gly Asp Ser
595 600 605

Gln Arg Leu Asp Leu Glu Asn Ala Val Leu Met Gln Glu Leu Met Ala
610 615 620

Met Lys Glu Glu Met Ala Glu Leu Lys Ala Gln Leu Tyr Leu Leu Glu
625 630 635 640

Lys Glu Lys Lys Ala Leu Glu Leu Lys Leu Ser Thr Arg Glu Ala Gln
645 650 655

Glu Gln Ala Tyr Leu Val His Ile Glu His Leu Lys Ser Glu Val Glu
660 665 670

Glu Gln Lys Glu Gln Arg Met Arg Ser Leu Ser Ser Thr Ser Ser Gly
675 680 685

Ser Lys Asp Lys Pro Gly Lys Glu Cys Ala Asp Ala Ala Ser Pro Ala
690 695 700

Leu Ser Leu Ala Glu Leu Arg Thr Thr Cys Ser Glu Asn Glu Leu Ala
705 710 715 720

Ala Glu Phe Thr Asn Ala Ile Arg Arg Glu Lys Lys Leu Lys Ala Arg
725 730 735

Val Gln Glu Leu Val Ser Ala Leu Glu Arg Leu Thr Lys Ser Ser Glu
740 745 750

Ile Arg His Gln Gln Ser Ala Glu Phe Val Asn Asp Leu Lys Arg Ala
755 760 765

Asn Ser Asn Leu Val Ala Ala Tyr Glu Lys Ala Lys Lys Lys His Gln
770 775 780

Asn Lys Leu Lys Lys Leu Glu Ser Gln Met Met Ala Met Val Glu Arg
785 790 795 800

His Glu Thr Gln Val Arg Met Leu Lys Gln Arg Ile Ala Leu Leu Glu
805 810 815

Glu Glu Asn Ser Arg Pro His Thr Asn Glu Thr Ser Leu
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gcggtcgcc atg gac cgc cca gat gag ggg cct ccg gcc aag acc cgc cgc 171
Met Asp Arg Pro Asp Glu Gly Pro Pro Ala Lys Thr Arg Arg
1 5 10

ctg agc agc tcc gag tct cca cag cgc gac ccg ccc ccg ccg ccg ccg 219
Leu Ser Ser Ser Glu Ser Pro Gln Arg Asp Pro Pro Pro Pro Pro Pro
15 20 25 30

ccg ccg ccg ctc ctc cga ctg ccg ctg cct cca ccc cag cag cgc ccg 267
Pro Pro Pro Leu Leu Arg Leu Pro Leu Pro Pro Pro Gln Gln Arg Pro
35 40 45

agg ctc cag gag gaa acg gag gcg gca cag gtg ctg gcc gat atg agg 315
Arg Leu Gln Glu Glu Thr Glu Ala Ala Gln Val Leu Ala Asp Met Arg
50 55 60

ggg gtg gga ctg ggc ccc gcg ctg ccc ccg ccg cct ccc tat gtc att 363
Gly Val Gly Leu Gly Pro Ala Leu Pro Pro Pro Pro Pro Tyr Val Ile
65 70 75

ctc gag gag ggg ggg atc cgc gca tac ttc acg ctc ggt gct gag tgt 411
Leu Glu Glu Gly Gly Ile Arg Ala Tyr Phe Thr Leu Gly Ala Glu Cys
80 85 90

ccc ggc tgg gat tct acc atc gag tcg ggg tat ggg gag gcg ccc ccg 459
Pro Gly Trp Asp Ser Thr Ile Glu Ser Gly Tyr Gly Glu Ala Pro Pro

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95                  100                 105                 110

ccc acg gag agc ctg gaa gca ctc ccc act cct gag gcc tcg ggg ggg       507
Pro Thr Glu Ser Leu Glu Ala Leu Pro Thr Pro Glu Ala Ser Gly Gly
                115                 120                 125

agc ctg gaa atc gat ttt cag gtt gta cag tcg agc agt ttt ggt gga       555
Ser Leu Glu Ile Asp Phe Gln Val Val Gln Ser Ser Ser Phe Gly Gly
            130                 135                 140

gag ggg gcc cta gaa acc tgt agc gca gtg ggg tgg gcg ccc cag agg       603
Glu Gly Ala Leu Glu Thr Cys Ser Ala Val Gly Trp Ala Pro Gln Arg
        145                 150                 155

tta gtt gac ccg aag agc aag gaa gag gcg atc atc ata gtg gag gat       651
Leu Val Asp Pro Lys Ser Lys Glu Glu Ala Ile Ile Ile Val Glu Asp
    160                 165                 170

gag gat gag gat gag cgg gag agt atg agg agc agc agg agg cgg cgg       699
Glu Asp Glu Asp Glu Arg Glu Ser Met Arg Ser Ser Arg Arg Arg Arg
175                 180                 185                 190

cgg cgg cgg agg agg aag cag agg aag gtg aag agg gaa agc aga gag       747
Arg Arg Arg Arg Arg Lys Gln Arg Lys Val Lys Arg Glu Ser Arg Glu
                195                 200                 205

aga aat gcc gag agg atg gag agc atc ctg cag gca ctg gag gat att       795
Arg Asn Ala Glu Arg Met Glu Ser Ile Leu Gln Ala Leu Glu Asp Ile
            210                 215                 220

cag ctg gat ctg gag gca gtg aac atc aag gca ggc aaa gcc ttc ctg       843
Gln Leu Asp Leu Glu Ala Val Asn Ile Lys Ala Gly Lys Ala Phe Leu
        225                 230                 235

cgt ctc aag cgc aag ttc atc cag atg cga aga ccc ttc ctg gag cgc       891
Arg Leu Lys Arg Lys Phe Ile Gln Met Arg Arg Pro Phe Leu Glu Arg
    240                 245                 250

aga gac ctc atc atc cag cat atc cca ggc ttc tgg gtc aaa gca ttc       939
Arg Asp Leu Ile Ile Gln His Ile Pro Gly Phe Trp Val Lys Ala Phe
255                 260                 265                 270

ctc aac cac ccc aga att tca att ttg atc aac cga cgt gat gaa gac       987
Leu Asn His Pro Arg Ile Ser Ile Leu Ile Asn Arg Arg Asp Glu Asp
                275                 280                 285

att ttc cgc tac ttg acc aat ctg cag gta cag gat ctc aga cat atc      1035
Ile Phe Arg Tyr Leu Thr Asn Leu Gln Val Gln Asp Leu Arg His Ile
            290                 295                 300

tcc atg ggc tac aaa atg aag ctg tac ttc cag act aac ccc tac ttc      1083
Ser Met Gly Tyr Lys Met Lys Leu Tyr Phe Gln Thr Asn Pro Tyr Phe
        305                 310                 315

aca aac atg gtg att gtc aag gag ttc cag cgc aac cgc tca ggc cgg      1131
Thr Asn Met Val Ile Val Lys Glu Phe Gln Arg Asn Arg Ser Gly Arg
    320                 325                 330

ctg gtg tct cac tca acc cca atc cgc tgg cac cgg ggc cag gaa ccc      1179
Leu Val Ser His Ser Thr Pro Ile Arg Trp His Arg Gly Gln Glu Pro
335                 340                 345                 350

cag gcc cgt cgt cac ggg aac cag gat gcg agc cac agc ttt ttc agc      1227
Gln Ala Arg Arg His Gly Asn Gln Asp Ala Ser His Ser Phe Phe Ser
                355                 360                 365

tgg ttc tca aac cat agc ctc cca gag gct gac agg att gct gag att      1275
Trp Phe Ser Asn His Ser Leu Pro Glu Ala Asp Arg Ile Ala Glu Ile
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            370                 375                 380

atc aag aat gat ctg tgg gtt aac cct cta cgc tac tac ctg aga gaa       1323
Ile Lys Asn Asp Leu Trp Val Asn Pro Leu Arg Tyr Tyr Leu Arg Glu
        385                 390                 395

agg ggc tcc agg ata aag aga aag aag caa gaa atg aag aaa cgt aaa       1371
Arg Gly Ser Arg Ile Lys Arg Lys Lys Gln Glu Met Lys Lys Arg Lys
    400                 405                 410

acc agg ggc aga tgt gag gtg gtg atc atg gaa gac gcc cct gac tat       1419
Thr Arg Gly Arg Cys Glu Val Val Ile Met Glu Asp Ala Pro Asp Tyr
415                 420                 425                 430

tat gca gtg gaa gac att ttc agc gag atc tca gac att gat gag aca       1467
Tyr Ala Val Glu Asp Ile Phe Ser Glu Ile Ser Asp Ile Asp Glu Thr
                435                 440                 445

att cat gac atc aag atc tct gac ttc atg gag acc acc gac tac ttc       1515
Ile His Asp Ile Lys Ile Ser Asp Phe Met Glu Thr Thr Asp Tyr Phe
            450                 455                 460

gag acc act gac aat gag ata act gac atc aat gag aac atc tgc gac       1563
Glu Thr Thr Asp Asn Glu Ile Thr Asp Ile Asn Glu Asn Ile Cys Asp
        465                 470                 475

agc gag aat cct gac cac aat gag gtc ccc aac aac gag acc act gat       1611
Ser Glu Asn Pro Asp His Asn Glu Val Pro Asn Asn Glu Thr Thr Asp
    480                 485                 490

aac aac gag agt gct gat gac cac gaa acc act gac aac aat gag agt       1659
Asn Asn Glu Ser Ala Asp Asp His Glu Thr Thr Asp Asn Asn Glu Ser
495                 500                 505                 510

gca gat gac aac aac gag aat cct gaa gac aat aac aag aac act gat       1707
Ala Asp Asp Asn Asn Glu Asn Pro Glu Asp Asn Asn Lys Asn Thr Asp
                515                 520                 525

gac aac gaa gag aac cct aac aac aac gag aac act tac ggc aac aac       1755
Asp Asn Glu Glu Asn Pro Asn Asn Asn Glu Asn Thr Tyr Gly Asn Asn
            530                 535                 540

ttc ttc aaa ggt ggc ttc tgg ggc agc cat ggc aac aac cag gac agc       1803
Phe Phe Lys Gly Gly Phe Trp Gly Ser His Gly Asn Asn Gln Asp Ser
        545                 550                 555

agc gac agt gac aat gaa gca gat gag gcc agt gat gat gaa gat aat       1851
Ser Asp Ser Asp Asn Glu Ala Asp Glu Ala Ser Asp Asp Glu Asp Asn
    560                 565                 570

gat ggc aac gaa ggt gac aat gag ggc agt gat gat gat ggc aat gaa       1899
Asp Gly Asn Glu Gly Asp Asn Glu Gly Ser Asp Asp Asp Gly Asn Glu
575                 580                 585                 590

ggt gac aat gaa ggc agc gat gat gac gac aga gac att gag tac tat       1947
Gly Asp Asn Glu Gly Ser Asp Asp Asp Asp Arg Asp Ile Glu Tyr Tyr
                595                 600                 605

gag aaa gtt att gaa gac ttt gac aag gat cag gct gac tac gag gac       1995
Glu Lys Val Ile Glu Asp Phe Asp Lys Asp Gln Ala Asp Tyr Glu Asp
            610                 615                 620

gtg ata gag atc atc tca gac gaa tca gtg gaa gaa gag ggc att gag       2043
Val Ile Glu Ile Ile Ser Asp Glu Ser Val Glu Glu Glu Gly Ile Glu
        625                 630                 635

gaa ggc atc cag caa gat gag gac atc tat gag gaa gga aac tat gag       2091
Glu Gly Ile Gln Gln Asp Glu Asp Ile Tyr Glu Glu Gly Asn Tyr Glu
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    640                 645                 650

gag gaa gga agt gaa gat gtc tgg gaa gaa ggg gaa gat tcg gac gac      2139
Glu Glu Gly Ser Glu Asp Val Trp Glu Glu Gly Glu Asp Ser Asp Asp
655                 660                 665                 670

tct gac cta gag gat gtg ctt cag gtc cca aac ggt tgg gcc aat ccg      2187
Ser Asp Leu Glu Asp Val Leu Gln Val Pro Asn Gly Trp Ala Asn Pro
                675                 680                 685

ggg aag agg ggg aaa acc gga taagggtttt ccccttttgg ggatcacctc        2238
Gly Lys Arg Gly Lys Thr Gly
            690

tctgtatccc ccacccacta tcccatttgc cctcctcctc agctagggcc acgcggcccc    2298

acattgcact tctgggggt gaccgacttc gtacacgggt ttaaagttta tttttatggt     2358

ttagtcattg cagagttctt attttggggg gagggaaagg gggctagtcc ccttcttttg    2418

gccctccgcc cccgcaggct tctgtgtgct gctaactgta tttattgtga tgccttggtc    2478

agggccccctc tacccacttc tcccagtcag ttgtggcccc agcccctctc cctgtgctgt   2538

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cgcagtgccc atggaggcgc tgctgccacc ttcctctccc aagttctttc tccatccctc    2658

tcctcttccc gccgcgccgc tagcccgcct cggtgtctat gcaaggccgc ttcgccattg    2718

cggtattctt tgcggtattc ttgtccccgt cccccagaag gctcgcctct ccccgtggac    2778

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            20                  25                  30

Pro Leu Leu Arg Leu Pro Leu Pro Pro Pro Gln Gln Arg Pro Arg Leu
        35                  40                  45

Gln Glu Glu Thr Glu Ala Ala Gln Val Leu Ala Asp Met Arg Gly Val
    50                  55                  60

Gly Leu Gly Pro Ala Leu Pro Pro Pro Pro Pro Tyr Val Ile Leu Glu
65                  70                  75                  80

Glu Gly Gly Ile Arg Ala Tyr Phe Thr Leu Gly Ala Glu Cys Pro Gly
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85 90 95

Trp Asp Ser Thr Ile Glu Ser Gly Tyr Gly Glu Ala Pro Pro Pro Thr
100 105 110

Glu Ser Leu Glu Ala Leu Pro Thr Pro Glu Ala Ser Gly Gly Ser Leu
115 120 125

Glu Ile Asp Phe Gln Val Val Gln Ser Ser Ser Phe Gly Gly Glu Gly
130 135 140

Ala Leu Glu Thr Cys Ser Ala Val Gly Trp Ala Pro Gln Arg Leu Val
145 150 155 160

Asp Pro Lys Ser Lys Glu Glu Ala Ile Ile Ile Val Glu Asp Glu Asp
165 170 175

Glu Asp Glu Arg Glu Ser Met Arg Ser Ser Arg Arg Arg Arg Arg Arg
180 185 190

Arg Arg Arg Lys Gln Arg Lys Val Lys Arg Glu Ser Arg Glu Arg Asn
195 200 205

Ala Glu Arg Met Glu Ser Ile Leu Gln Ala Leu Glu Asp Ile Gln Leu
210 215 220

Asp Leu Glu Ala Val Asn Ile Lys Ala Gly Lys Ala Phe Leu Arg Leu
225 230 235 240

Lys Arg Lys Phe Ile Gln Met Arg Arg Pro Phe Leu Glu Arg Arg Asp
245 250 255

Leu Ile Ile Gln His Ile Pro Gly Phe Trp Val Lys Ala Phe Leu Asn
260 265 270

His Pro Arg Ile Ser Ile Leu Ile Asn Arg Arg Asp Glu Asp Ile Phe
275 280 285

Arg Tyr Leu Thr Asn Leu Gln Val Gln Asp Leu Arg His Ile Ser Met
290 295 300

Gly Tyr Lys Met Lys Leu Tyr Phe Gln Thr Asn Pro Tyr Phe Thr Asn
305 310 315 320

Met Val Ile Val Lys Glu Phe Gln Arg Asn Arg Ser Gly Arg Leu Val
325 330 335

Ser His Ser Thr Pro Ile Arg Trp His Arg Gly Gln Glu Pro Gln Ala
340 345 350

Arg Arg His Gly Asn Gln Asp Ala Ser His Ser Phe Phe Ser Trp Phe

355 360 365

Ser Asn His Ser Leu Pro Glu Ala Asp Arg Ile Ala Glu Ile Ile Lys
370 375 380

Asn Asp Leu Trp Val Asn Pro Leu Arg Tyr Tyr Leu Arg Glu Arg Gly
385 390 395 400

Ser Arg Ile Lys Arg Lys Lys Gln Glu Met Lys Lys Arg Lys Thr Arg
405 410 415

Gly Arg Cys Glu Val Val Ile Met Glu Asp Ala Pro Asp Tyr Tyr Ala
420 425 430

Val Glu Asp Ile Phe Ser Glu Ile Ser Asp Ile Asp Glu Thr Ile His
435 440 445

Asp Ile Lys Ile Ser Asp Phe Met Glu Thr Thr Asp Tyr Phe Glu Thr
450 455 460

Thr Asp Asn Glu Ile Thr Asp Ile Asn Glu Asn Ile Cys Asp Ser Glu
465 470 475 480

Asn Pro Asp His Asn Glu Val Pro Asn Asn Glu Thr Thr Asp Asn Asn
485 490 495

Glu Ser Ala Asp Asp His Glu Thr Thr Asp Asn Asn Glu Ser Ala Asp
500 505 510

Asp Asn Asn Glu Asn Pro Glu Asp Asn Asn Lys Asn Thr Asp Asp Asn
515 520 525

Glu Glu Asn Pro Asn Asn Asn Glu Asn Thr Tyr Gly Asn Asn Phe Phe
530 535 540

Lys Gly Gly Phe Trp Gly Ser His Gly Asn Asn Gln Asp Ser Ser Asp
545 550 555 560

Ser Asp Asn Glu Ala Asp Glu Ala Ser Asp Asp Glu Asp Asn Asp Gly
565 570 575

Asn Glu Gly Asp Asn Glu Gly Ser Asp Asp Asp Gly Asn Glu Gly Asp
580 585 590

Asn Glu Gly Ser Asp Asp Asp Asp Arg Asp Ile Glu Tyr Tyr Glu Lys
595 600 605

Val Ile Glu Asp Phe Asp Lys Asp Gln Ala Asp Tyr Glu Asp Val Ile
610 615 620

Glu Ile Ile Ser Asp Glu Ser Val Glu Glu Glu Gly Ile Glu Glu Gly

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625                 630                 635                 640

Ile Gln Gln Asp Glu Asp Ile Tyr Glu Glu Gly Asn Tyr Glu Glu Glu
                645                 650                 655

Gly Ser Glu Asp Val Trp Glu Glu Gly Glu Asp Ser Asp Asp Ser Asp
            660                 665                 670

Leu Glu Asp Val Leu Gln Val Pro Asn Gly Trp Ala Asn Pro Gly Lys
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Arg Gly Lys Thr Gly
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ccgcacgctg agccctccgc ccgcgagccg cgctcagctc gggggtgatt agttgctttt     240

tgttgttttt taatttgggc cgcggggagg gggaggaggg gcaggtgctg caggctcccc     300

cccctccccg cctcgggcca gccgcggcgg cgcgactcgg gctccggacc cgggcactgc     360

tggcggctgg agcggagcgc accgcggcgg tggtgcccag agcggagcgc agctccctgc     420

cccgcccctc cccctcggcc tcgcggcgac ggcggcggtg gcggcttgga cgactcggag     480

agccgagtga agacatttcc acctggacac ctgaccatgt gcctgccctg agcagcgagg     540

cccaccaggc atctctgttg tgggcagcag ggccaggtcc tggtctgtgg accctcggca     600

gttggcaggc tccctctgca gtggggtctg ggcctcggcc ccaccatgtc gagcctcggc     660

ggtggctccc aggatgccgg cggcagtagc agcagcagca ccaatggcag cggtggcagt     720

ggcagcagtg gcccaaaggc aggagcagca gacaagagtg cagtggtggc tgccgccgca     780

ccagcctcag tggcagatga cacaccaccc cccgagcgtc ggaacaagag cggtatcatc     840
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agtgagcccc tcaacaagag cctgcgccgc tcccgcccgc tctcccacta ctcttctttt    900

ggcagcagtg gtggtagtgg cggtggcagc atg atg ggc gga gag tct gct gac     954
                                 Met Met Gly Gly Glu Ser Ala Asp
                                 1               5

aag gcc act gcg gct gca gcc gct gcc tcc ctg ttg gcc aat ggg cat     1002
Lys Ala Thr Ala Ala Ala Ala Ala Ala Ser Leu Leu Ala Asn Gly His
    10                  15                  20

gac ctg gcg gcg gcc atg gcg gtg gac aaa agc aac cct acc tca aag     1050
Asp Leu Ala Ala Ala Met Ala Val Asp Lys Ser Asn Pro Thr Ser Lys
25                  30                  35                  40

cac aaa agt ggt gct gtg gcc agc ctg ctg agc aag gca gag cgg gcc     1098
His Lys Ser Gly Ala Val Ala Ser Leu Leu Ser Lys Ala Glu Arg Ala
                45                  50                  55

acg gag ctg gca gcc gag gga cag ctg acg ctg cag cag ttt gcg cag     1146
Thr Glu Leu Ala Ala Glu Gly Gln Leu Thr Leu Gln Gln Phe Ala Gln
            60                  65                  70

tcc aca gag atg ctg aag cgc gtg gtg cag gag cat ctc ccg ctg atg     1194
Ser Thr Glu Met Leu Lys Arg Val Val Gln Glu His Leu Pro Leu Met
        75                  80                  85

agc gag gcg ggt gct ggc ctg cct gac atg gag gct gtg gca ggt gcc     1242
Ser Glu Ala Gly Ala Gly Leu Pro Asp Met Glu Ala Val Ala Gly Ala
    90                  95                  100

gaa gcc ctc aat ggc cag tcc gac ttc ccc tac ctg ggc gct ttc ccc     1290
Glu Ala Leu Asn Gly Gln Ser Asp Phe Pro Tyr Leu Gly Ala Phe Pro
105                 110                 115                 120

atc aac cca ggc ctc ttc att atg acc ccg gca ggt gtg ttc ctg gcc     1338
Ile Asn Pro Gly Leu Phe Ile Met Thr Pro Ala Gly Val Phe Leu Ala
                125                 130                 135

gag agc gcg ctg cac atg gcg ggc ctg gct gag tac ccc atg cag gga     1386
Glu Ser Ala Leu His Met Ala Gly Leu Ala Glu Tyr Pro Met Gln Gly
            140                 145                 150

gag ctg gcc tct gcc atc agc tcc ggc aag aag aag cgg aaa cgc tgc     1434
Glu Leu Ala Ser Ala Ile Ser Ser Gly Lys Lys Lys Arg Lys Arg Cys
        155                 160                 165

ggc atg tgc gcg ccc tgc cgg cgg cgc atc aac tgc gag cag tgc agc     1482
Gly Met Cys Ala Pro Cys Arg Arg Arg Ile Asn Cys Glu Gln Cys Ser
    170                 175                 180

agt tgt agg aat cga aag act ggc cat cag att tgc aaa ttc aga aaa     1530
Ser Cys Arg Asn Arg Lys Thr Gly His Gln Ile Cys Lys Phe Arg Lys
185                 190                 195                 200

tgt gag gaa ctc aaa aag aag cct tcc gct gct ctg gag aag gtg atg     1578
Cys Glu Glu Leu Lys Lys Lys Pro Ser Ala Ala Leu Glu Lys Val Met
                205                 210                 215

ctt ccg acg gga gcc gcc ttc cgg tgg ttt cag tgacggcggc ggaacccaaa   1631
Leu Pro Thr Gly Ala Ala Phe Arg Trp Phe Gln
            220                 225

gctgccctct ccgtgcaatg tcactgctcg tgtggtctcc agcaagggat tcgggcgaag   1691

acaaacggat gcacccgtct ttagaaccaa aaatattctc tcacagattt cattcctgtt   1751

tttatatata tattttttgt tgtcgtttta acatctccac gtccctagca taaaaagaaa   1811
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aagaaaaaaa tttaaactgc tttttcggaa gaacaacaac aaaaaagagg taaagacgaa    1871
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atgtcgatgt tgtctgtgca ggagatgcag ttttgtgta gagaatgtaa attttctgta     1991
accttttgaa atctagttac taataagcac tactgtaatt tagcacagtt taactccacc    2051
ctcatttaaa cttcctttga ttctttccga ccatgaaata gtgcatagtt tgcctggaga    2111
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cagaagaaag ggcttctttg cgtggtcccc tgctggtggg ggtgggtccc caggggggccc   2471
cctgcggcct gggccccccct gcccacggcc agcttcctgc tgatgaacat gctgtttgta   2531
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<213> NM_016463 HSPC195

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            20                  25                  30

Asp Lys Ser Asn Pro Thr Ser Lys His Lys Ser Gly Ala Val Ala Ser
        35                  40                  45

Leu Leu Ser Lys Ala Glu Arg Ala Thr Glu Leu Ala Ala Glu Gly Gln
    50                  55                  60

Leu Thr Leu Gln Gln Phe Ala Gln Ser Thr Glu Met Leu Lys Arg Val
65                  70                  75                  80

Val Gln Glu His Leu Pro Leu Met Ser Glu Ala Gly Ala Gly Leu Pro
                85                  90                  95

Asp Met Glu Ala Val Ala Gly Ala Glu Ala Leu Asn Gly Gln Ser Asp
            100                 105                 110
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Phe Pro Tyr Leu Gly Ala Phe Pro Ile Asn Pro Gly Leu Phe Ile Met
        115                 120                 125

Thr Pro Ala Gly Val Phe Leu Ala Glu Ser Ala Leu His Met Ala Gly
    130                 135                 140

Leu Ala Glu Tyr Pro Met Gln Gly Glu Leu Ala Ser Ala Ile Ser Ser
145                 150                 155                 160

Gly Lys Lys Lys Arg Lys Arg Cys Gly Met Cys Ala Pro Cys Arg Arg
                165                 170                 175

Arg Ile Asn Cys Glu Gln Cys Ser Ser Cys Arg Asn Arg Lys Thr Gly
            180                 185                 190

His Gln Ile Cys Lys Phe Arg Lys Cys Glu Glu Leu Lys Lys Lys Pro
        195                 200                 205

Ser Ala Ala Leu Glu Lys Val Met Leu Pro Thr Gly Ala Ala Phe Arg
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Trp Phe Gln
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Met Thr Glu Tyr Leu Asn Phe Glu Lys Ser Ser Ser Val Ser Arg Tyr
1               5                   10                  15

gga gcc tct caa gtt gaa gat atg ggg aat ata att tta gca atg att       153
Gly Ala Ser Gln Val Glu Asp Met Gly Asn Ile Ile Leu Ala Met Ile
            20                  25                  30

tca gag cct tat aat cac agg ttt tca gat cca gag aga gtg aat tac       201
Ser Glu Pro Tyr Asn His Arg Phe Ser Asp Pro Glu Arg Val Asn Tyr
        35                  40                  45
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aag ttt gaa agt gga act tgc agc aag atg gaa ctt att gat gat aac        249
Lys Phe Glu Ser Gly Thr Cys Ser Lys Met Glu Leu Ile Asp Asp Asn
    50                  55                  60

acc gta gtc agg gca cga ggt tta cca tgg cag tct tca gat caa gat        297
Thr Val Val Arg Ala Arg Gly Leu Pro Trp Gln Ser Ser Asp Gln Asp
65                  70                  75                  80

att gca aga ttc ttc aaa gga ctc aat att gcc aag gga ggt gca gca        345
Ile Ala Arg Phe Phe Lys Gly Leu Asn Ile Ala Lys Gly Gly Ala Ala
                85                  90                  95

ctt tgt ctg aat gct cag ggt cga agg aac gga gaa gct ctg gtt agg        393
Leu Cys Leu Asn Ala Gln Gly Arg Arg Asn Gly Glu Ala Leu Val Arg
            100                 105                 110

ttt gta agt gag gag cac cga gac cta gca cta cag agg cac aaa cat        441
Phe Val Ser Glu Glu His Arg Asp Leu Ala Leu Gln Arg His Lys His
        115                 120                 125

cac atg ggg acc cgg tat att gag gtt tac aaa gca aca ggt gaa gat        489
His Met Gly Thr Arg Tyr Ile Glu Val Tyr Lys Ala Thr Gly Glu Asp
    130                 135                 140

ttc ctt aaa att gct ggt ggt act tcc aat gag gta gcc cag ttt ctc        537
Phe Leu Lys Ile Ala Gly Gly Thr Ser Asn Glu Val Ala Gln Phe Leu
145                 150                 155                 160

tcc aag gaa aat caa gtc att gtt cgc atg cgg ggg ctc cct ttc acg        585
Ser Lys Glu Asn Gln Val Ile Val Arg Met Arg Gly Leu Pro Phe Thr
                165                 170                 175

gcc aca gct gaa gaa gtg gtg gcc ttc ttt gga cag cat tgc cct att        633
Ala Thr Ala Glu Glu Val Val Ala Phe Phe Gly Gln His Cys Pro Ile
            180                 185                 190

act ggg gga aag gaa ggc atc ctc ttt gtc acc tac cca gat ggt agg        681
Thr Gly Gly Lys Glu Gly Ile Leu Phe Val Thr Tyr Pro Asp Gly Arg
        195                 200                 205

cca aca ggg gac gct ttt gtc ctc ttt gcc tgt gag gaa tat gca cag        729
Pro Thr Gly Asp Ala Phe Val Leu Phe Ala Cys Glu Glu Tyr Ala Gln
    210                 215                 220

aat gcg ttg agg aag cat aaa gac ttg ttg ggt aaa aga tac att gaa        777
Asn Ala Leu Arg Lys His Lys Asp Leu Leu Gly Lys Arg Tyr Ile Glu
225                 230                 235                 240

ctc ttc agg agc aca gca gct gaa gtt cag cag gtg ctg aat cga ttc        825
Leu Phe Arg Ser Thr Ala Ala Glu Val Gln Gln Val Leu Asn Arg Phe
                245                 250                 255

tcc tcg gcc cct ctc att cca ctt cca acc cct ccc att att cca gta        873
Ser Ser Ala Pro Leu Ile Pro Leu Pro Thr Pro Pro Ile Ile Pro Val
            260                 265                 270

cta cct cag caa ttt gtg ccc cct aca aat gtt aga gac tgt ata cgc        921
Leu Pro Gln Gln Phe Val Pro Pro Thr Asn Val Arg Asp Cys Ile Arg
        275                 280                 285

ctt cga ggt ctt ccc tat gca gcc aca att gag gac atc ctg gat ttc        969
Leu Arg Gly Leu Pro Tyr Ala Ala Thr Ile Glu Asp Ile Leu Asp Phe
    290                 295                 300

ctg ggg gag ttc gcc aca gat att cgt act cat ggg gtt cac atg gtt       1017
Leu Gly Glu Phe Ala Thr Asp Ile Arg Thr His Gly Val His Met Val
305                 310                 315                 320
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ttg aat cac cag ggc cgc cca tca gga gat gcc ttt atc cag atg aag     1065
Leu Asn His Gln Gly Arg Pro Ser Gly Asp Ala Phe Ile Gln Met Lys
            325                 330                 335

tct gcg gac aga gca ttt atg gct gca cag aag tgt cat aaa aaa aaa     1113
Ser Ala Asp Arg Ala Phe Met Ala Ala Gln Lys Cys His Lys Lys Lys
        340                 345                 350

cat gaa gga cag ata tgt tgaagtcttt cagtgttcag ctgaggagat            1161
His Glu Gly Gln Ile Cys
    355

gaactttgtg ttaatggggg gcactttaaa tcgaaatggc ttatccccac cgccatgtaa   1221

gttaccatgc ctgtctcctc cctcctacac atttccagct cctgctgcag ttattcctac   1281

agaagctgcc atttaccagc cctctgtgat tttgaatcca cgagcactgc agccctccac   1341

agcgtactac ccagcaggca ctcagctctt catgaactac acagcgtact atcccagccc   1401

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tccacagcct ggcacggtgg tcagaatgca gggcctggcc tacaatactg gagttaagga   1521

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ccagacacaa gaaaacttct agcaaattca ggggaagttt gtctacactc aggctgcagt   1641

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agtttgagct agtgaagcca aatcgtaact tacagcaagc agcatgcagc atacctggct   1761

ctttgctgat tgcaaatagg catttaaaat gtgaatttgg aatcagatgt ctccattact   1821

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ctcttttctc ttcatttccc tgtcttctgc ataatcatgc cttcttgcta agtaattcaa   2001

gcataagatc ttggaataat aaaatcacaa tcttaggaga aagaataaaa ttgttatttt   2061

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<212> PRT

<213> NM_017697 FLJ20171

<400> 10

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Gly Ala Ser Gln Val Glu Asp Met Gly Asn Ile Ile Leu Ala Met Ile
            20                  25                  30
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Ser Glu Pro Tyr Asn His Arg Phe Ser Asp Pro Glu Arg Val Asn Tyr
        35                  40                  45

Lys Phe Glu Ser Gly Thr Cys Ser Lys Met Glu Leu Ile Asp Asp Asn
    50                  55                  60

Thr Val Val Arg Ala Arg Gly Leu Pro Trp Gln Ser Ser Asp Gln Asp
65                  70                  75                  80

Ile Ala Arg Phe Phe Lys Gly Leu Asn Ile Ala Lys Gly Gly Ala Ala
                85                  90                  95

Leu Cys Leu Asn Ala Gln Gly Arg Arg Asn Gly Glu Ala Leu Val Arg
            100                 105                 110

Phe Val Ser Glu Glu His Arg Asp Leu Ala Leu Gln Arg His Lys His
        115                 120                 125

His Met Gly Thr Arg Tyr Ile Glu Val Tyr Lys Ala Thr Gly Glu Asp
    130                 135                 140

Phe Leu Lys Ile Ala Gly Gly Thr Ser Asn Glu Val Ala Gln Phe Leu
145                 150                 155                 160

Ser Lys Glu Asn Gln Val Ile Val Arg Met Arg Gly Leu Pro Phe Thr
                165                 170                 175

Ala Thr Ala Glu Glu Val Val Ala Phe Phe Gly Gln His Cys Pro Ile
            180                 185                 190

Thr Gly Gly Lys Glu Gly Ile Leu Phe Val Thr Tyr Pro Asp Gly Arg
        195                 200                 205

Pro Thr Gly Asp Ala Phe Val Leu Phe Ala Cys Glu Glu Tyr Ala Gln
    210                 215                 220

Asn Ala Leu Arg Lys His Lys Asp Leu Leu Gly Lys Arg Tyr Ile Glu
225                 230                 235                 240

Leu Phe Arg Ser Thr Ala Ala Glu Val Gln Gln Val Leu Asn Arg Phe
                245                 250                 255

Ser Ser Ala Pro Leu Ile Pro Leu Pro Thr Pro Pro Ile Ile Pro Val
            260                 265                 270

Leu Pro Gln Gln Phe Val Pro Pro Thr Asn Val Arg Asp Cys Ile Arg
        275                 280                 285

Leu Arg Gly Leu Pro Tyr Ala Ala Thr Ile Glu Asp Ile Leu Asp Phe
    290                 295                 300
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Leu Gly Glu Phe Ala Thr Asp Ile Arg Thr His Gly Val His Met Val
305                 310                 315                 320

Leu Asn His Gln Gly Arg Pro Ser Gly Asp Ala Phe Ile Gln Met Lys
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Ser Ala Asp Arg Ala Phe Met Ala Ala Gln Lys Cys His Lys Lys Lys
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His Glu Gly Gln Ile Cys
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                     Met Ser Ala Gly Gly Ala Ser Val Pro Pro Pro
                     1               5                   10

ccg aac ccc gcc gtg tcc ttc ccg ccg ccc cgg gtc acc ctg ccc gcc        160
Pro Asn Pro Ala Val Ser Phe Pro Pro Pro Arg Val Thr Leu Pro Ala
            15                  20                  25

ggc ccc gac atc ctg cgg acc tac tcg ggc gcc ttc gtc tgc ctg gag        208
Gly Pro Asp Ile Leu Arg Thr Tyr Ser Gly Ala Phe Val Cys Leu Glu
        30                  35                  40

att ctg ttc ggg ggt ctt gtc tgg att ttg gtt gcc tcc tcc aat gtt        256
Ile Leu Phe Gly Gly Leu Val Trp Ile Leu Val Ala Ser Ser Asn Val
    45                  50                  55

cct cta cct cta cta caa gga tgg gtc atg ttt gtg tcc gtg aca gcg        304
Pro Leu Pro Leu Leu Gln Gly Trp Val Met Phe Val Ser Val Thr Ala
60                  65                  70                  75

ttt ttc ttt tcg ctc ctc ttt ctg ggc atg ttc ctc tct ggc atg gtg        352
Phe Phe Phe Ser Leu Leu Phe Leu Gly Met Phe Leu Ser Gly Met Val
                80                  85                  90

gct caa att gat gct aac tgg aac ttc ctg gat ttt gcc tac cat ttt        400
Ala Gln Ile Asp Ala Asn Trp Asn Phe Leu Asp Phe Ala Tyr His Phe
            95                  100                 105
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aca gta ttt gtc ttc tat ttt gga gcc ttt tta ttg gaa gca gca gcc      448
Thr Val Phe Val Phe Tyr Phe Gly Ala Phe Leu Leu Glu Ala Ala Ala
        110                 115                 120

aca tcc ctg cat gat ttg cat tgc aat aca acc ata acc ggg cag cca      496
Thr Ser Leu His Asp Leu His Cys Asn Thr Thr Ile Thr Gly Gln Pro
    125                 130                 135

ctc ctg agt gat aac cag tat aac ata aac gta gca gcc tca att ttt      544
Leu Leu Ser Asp Asn Gln Tyr Asn Ile Asn Val Ala Ala Ser Ile Phe
140                 145                 150                 155

gcc ttt atg acg aca gct tgt tat ggt tgc agt ttg ggt ctg gct tta      592
Ala Phe Met Thr Thr Ala Cys Tyr Gly Cys Ser Leu Gly Leu Ala Leu
                160                 165                 170

cga aga tgg cga ccg taacactcct tagaaactgg cagtcgtatg ttagtttcac      647
Arg Arg Trp Arg Pro
            175

ttgtctactt tatatgtctg atcaatttgg ataccatttt gtccagatgc aaaaacattc     707

caaaagtaat gtgtttagta gagagagact ctaagctcaa gttctggttt atttcatgga     767

tggaatgtta attttattat gatattaaag aaatggcctt ttattttaca tctctcccct     827

ttttcccttt ccccctttat tttcctcctt ttctttctga aagtttcctt ttatgtccat     887

aaaatacaaa tatattgttc ataaaaaatt agtatccctt ttgtttggtt gctgagtcac     947

ctgaacctta attttaattg gtaattacag cccctaaaaa aaacacattt caaataggct    1007

tcccactaaa ctctatattt tagtgtaaac caggaattgg cacacttttt ttagaatggg    1067

ccagatggta aatatttatg cttcacggtc catacagtct ctgtcacaac tattcagttc    1127

tgctagtata gcgtgaaagc agctatacac aatacagaaa tgaatgagtg tggttatgtt    1187

ctaataaaac ttatttataa aaacaagggg aggctgggtt tagcctgtgg gccatagttt    1247

gtcaaccact ggtgtaaaac cttagttata tatgatctgc attttcttga actgatcatt    1307

gaaaacttat aaacctaaca gaaaagccac ataatattta gtgtcattat gcaataatca    1367

cattgccttt gtgttaatag tcaaatactt acctttggag aatacttacc tttggaggaa    1427

tgtataaaat ttctcaggca gagtcctgga tataggaaaa agtaatttat gaagtaaact    1487

tcagttgctt aatcaaacta atgatagtct aacaactgag caagatcctc atctgagagt    1547

gcttaaaatg ggatccccag agaccattaa ccaatactgg aactggtatc tagctactga    1607

tgtcttactt tgagtttatt tatgcttcag aatacagttg tttgccctgt gcatgaatat    1667

acccatattt gtgtgtggat atgtgaagct tttccaaata gagctctcag aagaattaag    1727

tttttacttc taattatttt gcattacttt gagttaaatt tgaatagagt attaaatata    1787

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gtgacagaca aaatctgttt taaaatcata tccagcacaa aaactatttc tggctgaata    1907

gcacagaaaa gtattttaac ctacctgtag agatcctcgt catggaaagg tgccaaactg    1967

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attgttctac tttttcagcc ctttactttc tggctgaagc atccccttgg agtgccatgt    2087
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gtgcttaatg atcaagtgtt acttatctaa taatcctcta gaaagaaccc tgttagatct 2207

tggtttgtga taaaaatata aagacagaag acatgaggaa aaacaaaagg tttgaggaaa 2267

tcaggcatat gactttatac ttaacatcag atcttttcta taatatccta ctactttggt 2327

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Arg Thr Tyr Ser Gly Ala Phe Val Cys Leu Glu Ile Leu Phe Gly Gly
35 40 45

Leu Val Trp Ile Leu Val Ala Ser Ser Asn Val Pro Leu Pro Leu Leu
50 55 60

Gln Gly Trp Val Met Phe Val Ser Val Thr Ala Phe Phe Phe Ser Leu
65 70 75 80

Leu Phe Leu Gly Met Phe Leu Ser Gly Met Val Ala Gln Ile Asp Ala
85 90 95

Asn Trp Asn Phe Leu Asp Phe Ala Tyr His Phe Thr Val Phe Val Phe
100 105 110

Tyr Phe Gly Ala Phe Leu Leu Glu Ala Ala Ala Thr Ser Leu His Asp

115 120 125

Leu His Cys Asn Thr Thr Ile Thr Gly Gln Pro Leu Leu Ser Asp Asn
130 135 140

Gln Tyr Asn Ile Asn Val Ala Ala Ser Ile Phe Ala Phe Met Thr Thr
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Met Pro Arg Pro Glu Leu Pro Leu Pro Glu Gly Trp Glu Glu
1 5 10

gcg cgc gac ttc gac ggc aag gtc tac tac ata gac cac acg aac cgc 156
Ala Arg Asp Phe Asp Gly Lys Val Tyr Tyr Ile Asp His Thr Asn Arg
15 20 25 30

acc acc agc tgg atc gac ccg cgg gac agg tac acc aaa ccg ctc acc 204
Thr Thr Ser Trp Ile Asp Pro Arg Asp Arg Tyr Thr Lys Pro Leu Thr
35 40 45

ttt gct gac tgc att agt gat gag ttg ccg cta gga tgg gaa gag gca 252
Phe Ala Asp Cys Ile Ser Asp Glu Leu Pro Leu Gly Trp Glu Glu Ala
50 55 60

tat gac cca cag gtt gga gat tac ttc ata gac cac aac acc aaa acc 300
Tyr Asp Pro Gln Val Gly Asp Tyr Phe Ile Asp His Asn Thr Lys Thr
65 70 75

act cag att gag gat cct cga gta caa tgg cgg cgg gag cag gaa cat 348
Thr Gln Ile Glu Asp Pro Arg Val Gln Trp Arg Arg Glu Gln Glu His
80 85 90

atg ctg aag gat tac ctg gtg gtg gcc cag gag gct ctg agt gca caa 396
Met Leu Lys Asp Tyr Leu Val Val Ala Gln Glu Ala Leu Ser Ala Gln
95 100 105 110

aag gag atc tac cag gtg aag cag cag cgc ctg gag ctt gca cag cag 444

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Lys Glu Ile Tyr Gln Val Lys Gln Gln Arg Leu Glu Leu Ala Gln Gln
                115                 120                 125

gag tac cag caa ctg cat gcc gtc tgg gag cat aag ctg ggc tcc cag      492
Glu Tyr Gln Gln Leu His Ala Val Trp Glu His Lys Leu Gly Ser Gln
            130                 135                 140

gtc agc ttg gtc tct ggt tca tca tcc agc tcc aag tat gac cct gag      540
Val Ser Leu Val Ser Gly Ser Ser Ser Ser Ser Lys Tyr Asp Pro Glu
        145                 150                 155

atc ctg aaa gct gaa att gcc act gca aaa tcc cgg gtc aac aag ctg      588
Ile Leu Lys Ala Glu Ile Ala Thr Ala Lys Ser Arg Val Asn Lys Leu
    160                 165                 170

aag aga gag atg gtt cac ctc cag cac gag ctg cag ttc aaa gag cgt      636
Lys Arg Glu Met Val His Leu Gln His Glu Leu Gln Phe Lys Glu Arg
175                 180                 185                 190

ggc ttt cag acc ctg aag aaa atc gat aag aaa atg tct gat gct cag      684
Gly Phe Gln Thr Leu Lys Lys Ile Asp Lys Lys Met Ser Asp Ala Gln
                195                 200                 205

ggc agc tac aaa ctg gat gaa gct cag gct gtc ttg aga gaa aca aaa      732
Gly Ser Tyr Lys Leu Asp Glu Ala Gln Ala Val Leu Arg Glu Thr Lys
            210                 215                 220

gcc atc aaa aag gct att acc tgt ggg gaa aag gaa aag caa gat ctc      780
Ala Ile Lys Lys Ala Ile Thr Cys Gly Glu Lys Glu Lys Gln Asp Leu
        225                 230                 235

att aag agc ctt gcc atg ttg aag gac ggc ttc cgc act gac agg ggg      828
Ile Lys Ser Leu Ala Met Leu Lys Asp Gly Phe Arg Thr Asp Arg Gly
    240                 245                 250

tct cac tca gac ctg tgg tcc agc agc agc tct ctg gag agt tcg agt      876
Ser His Ser Asp Leu Trp Ser Ser Ser Ser Ser Leu Glu Ser Ser Ser
255                 260                 265                 270

ttc ccg cta ccg aaa cag tac ctg gat gtg agc tcc cag aca gac atc      924
Phe Pro Leu Pro Lys Gln Tyr Leu Asp Val Ser Ser Gln Thr Asp Ile
                275                 280                 285

tcg gga agc ttc ggc atc aac agc aac aat cag ttg gca gag aag gtc      972
Ser Gly Ser Phe Gly Ile Asn Ser Asn Asn Gln Leu Ala Glu Lys Val
            290                 295                 300

aga ttg cgc ctt cga tat gaa gag gct aag aga agg atc gcc aac ctg     1020
Arg Leu Arg Leu Arg Tyr Glu Glu Ala Lys Arg Arg Ile Ala Asn Leu
        305                 310                 315

aag atc cag ctg gcc aag ctt gac agt gag gcc tgg cct ggg gtg ctg     1068
Lys Ile Gln Leu Ala Lys Leu Asp Ser Glu Ala Trp Pro Gly Val Leu
    320                 325                 330

gac tca gag agg gac cgg ctg atc ctt atc aac gag aag gag gag ctg     1116
Asp Ser Glu Arg Asp Arg Leu Ile Leu Ile Asn Glu Lys Glu Glu Leu
335                 340                 345                 350

ctg aag gag atg cgc ttc atc agc ccc cgc aag tgg acc cag ggg gag     1164
Leu Lys Glu Met Arg Phe Ile Ser Pro Arg Lys Trp Thr Gln Gly Glu
                355                 360                 365

gtg gag cag ctg gag atg gcc cgg aag cgg ctg gaa aag gac ctg cag     1212
Val Glu Gln Leu Glu Met Ala Arg Lys Arg Leu Glu Lys Asp Leu Gln
            370                 375                 380
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gca gcc cgg gac acc cag agc aag gcg ctg acg gag agg tta aag tta      1260
Ala Ala Arg Asp Thr Gln Ser Lys Ala Leu Thr Glu Arg Leu Lys Leu
        385                 390                 395

aac agt aag agg aac cag ctt gtg aga gaa ctg gag gaa gcc acc cgg      1308
Asn Ser Lys Arg Asn Gln Leu Val Arg Glu Leu Glu Glu Ala Thr Arg
    400                 405                 410

cag gtg gca act ctg cac tcc cag ctg aaa agt ctc tca agc agc atg      1356
Gln Val Ala Thr Leu His Ser Gln Leu Lys Ser Leu Ser Ser Ser Met
415                 420                 425                 430

cag tcc ctg tcc tca ggc agc agc ccc gga tcc ctc acg tcc agc cgg      1404
Gln Ser Leu Ser Ser Gly Ser Ser Pro Gly Ser Leu Thr Ser Ser Arg
                435                 440                 445

ggc tcc ctg gtt gca tcc agc ctg gac tcc tcc act tca gcc agc ttc      1452
Gly Ser Leu Val Ala Ser Ser Leu Asp Ser Ser Thr Ser Ala Ser Phe
            450                 455                 460

act gac ctc tac tat gac ccc ttt gag cag ctg gac tca gag ctg cag      1500
Thr Asp Leu Tyr Tyr Asp Pro Phe Glu Gln Leu Asp Ser Glu Leu Gln
        465                 470                 475

agc aag gtg gag ttc ctg ctc ctg gag ggg gcc acc ggc ttc cgg ccc      1548
Ser Lys Val Glu Phe Leu Leu Leu Glu Gly Ala Thr Gly Phe Arg Pro
    480                 485                 490

tca ggc tgc atc acc acc atc cac gag gat gag gtg gcc aag acc cag      1596
Ser Gly Cys Ile Thr Thr Ile His Glu Asp Glu Val Ala Lys Thr Gln
495                 500                 505                 510

aag gca gag gga ggt ggc cgc ctg cag gct ctg cgt tcc ctg tct ggc      1644
Lys Ala Glu Gly Gly Gly Arg Leu Gln Ala Leu Arg Ser Leu Ser Gly
                515                 520                 525

acc cca aag tcc atg acc tcc cta tcc cca cgt tcc tct ctc tcc tcc      1692
Thr Pro Lys Ser Met Thr Ser Leu Ser Pro Arg Ser Ser Leu Ser Ser
            530                 535                 540

ccc tcc cca ccc tgt tcc cct ctc atg gct gac ccc ctc ctg gct ggt      1740
Pro Ser Pro Pro Cys Ser Pro Leu Met Ala Asp Pro Leu Leu Ala Gly
        545                 550                 555

gat gcc ttc ctc aac tcc ttg gag ttt gaa gac ccg gag ctg agt gcc      1788
Asp Ala Phe Leu Asn Ser Leu Glu Phe Glu Asp Pro Glu Leu Ser Ala
    560                 565                 570

act ctt tgt gaa ctg agc ctt ggt aac agc gcc cag gaa aga tac cgg      1836
Thr Leu Cys Glu Leu Ser Leu Gly Asn Ser Ala Gln Glu Arg Tyr Arg
575                 580                 585                 590

ctg gag gaa cca gga acg gag ggc aag cag ctg ggc caa gct gtg aat      1884
Leu Glu Glu Pro Gly Thr Glu Gly Lys Gln Leu Gly Gln Ala Val Asn
                595                 600                 605

acg gcc cag ggg tgt ggc ctg aaa gtg gcc tgt gtc tca gcc gcc gta      1932
Thr Ala Gln Gly Cys Gly Leu Lys Val Ala Cys Val Ser Ala Ala Val
            610                 615                 620

tcg gac gag tca gtg gct gga gac agt ggt gtg tac gag gct tcc gtg      1980
Ser Asp Glu Ser Val Ala Gly Asp Ser Gly Val Tyr Glu Ala Ser Val
        625                 630                 635

cag aga ctg ggt gct tca gaa gct gct gca ttt gac agt gac gaa tcg      2028
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Gln Arg Leu Gly Ala Ser Glu Ala Ala Ala Phe Asp Ser Asp Glu Ser
    640                 645                 650

gaa gca gtg ggt gcg acc cga att cag att gcc ctg aag tat gat gag     2076
Glu Ala Val Gly Ala Thr Arg Ile Gln Ile Ala Leu Lys Tyr Asp Glu
655                 660                 665                 670

aag aat aag caa ttt gca ata tta atc atc cag ctg agt aac ctt tct     2124
Lys Asn Lys Gln Phe Ala Ile Leu Ile Ile Gln Leu Ser Asn Leu Ser
                675                 680                 685

gct ctg ttg cag caa caa gac cag aaa gtg aat atc cgc gtg gct gtc     2172
Ala Leu Leu Gln Gln Gln Asp Gln Lys Val Asn Ile Arg Val Ala Val
            690                 695                 700

ctt cct tgc tct gaa agc aca acc tgc ctg ttc cgg acc cgg cct ctg     2220
Leu Pro Cys Ser Glu Ser Thr Thr Cys Leu Phe Arg Thr Arg Pro Leu
        705                 710                 715

gac gcc tca gac act cta gtg ttc aat gag gtg ttc tgg gta tcc atg     2268
Asp Ala Ser Asp Thr Leu Val Phe Asn Glu Val Phe Trp Val Ser Met
    720                 725                 730

tcc tat cca gcc ctt cac cag aag acc tta aga gtc gat gtc tgt acc     2316
Ser Tyr Pro Ala Leu His Gln Lys Thr Leu Arg Val Asp Val Cys Thr
735                 740                 745                 750

acc gac agg agc cat ctg gaa gag tgc ctg gga ggc gcc cag atc agc     2364
Thr Asp Arg Ser His Leu Glu Glu Cys Leu Gly Gly Ala Gln Ile Ser
                755                 760                 765

ctg gcg gag gtc tgc cgg tct ggg gag agg tcg act cgc tgg tac aac     2412
Leu Ala Glu Val Cys Arg Ser Gly Glu Arg Ser Thr Arg Trp Tyr Asn
            770                 775                 780

ctt ctc agc tac aaa tac ttg aag aag cag agc agg gag ctc aag cca     2460
Leu Leu Ser Tyr Lys Tyr Leu Lys Lys Gln Ser Arg Glu Leu Lys Pro
        785                 790                 795

gtg gga gtt atg gcc cct gcc tca ggg cct gcc agc acg gac gct gtg     2508
Val Gly Val Met Ala Pro Ala Ser Gly Pro Ala Ser Thr Asp Ala Val
    800                 805                 810

tct gct ctg ttg gaa cag aca gca gtg gag ctg gag aag agg cag gag     2556
Ser Ala Leu Leu Glu Gln Thr Ala Val Glu Leu Glu Lys Arg Gln Glu
815                 820                 825                 830

ggc agg agc agc aca cag aca ctg gaa gac agc tgg agg tat gag gag     2604
Gly Arg Ser Ser Thr Gln Thr Leu Glu Asp Ser Trp Arg Tyr Glu Glu
                835                 840                 845

acc agt gag aat gag gca gta gcc gag gaa gag gag gag gag gtg gag     2652
Thr Ser Glu Asn Glu Ala Val Ala Glu Glu Glu Glu Glu Glu Val Glu
            850                 855                 860

gag gag gag gga gaa gag gat gtt ttc acc gag aaa gcc tca cct gat     2700
Glu Glu Glu Gly Glu Glu Asp Val Phe Thr Glu Lys Ala Ser Pro Asp
        865                 870                 875

atg gat ggg tac cca gca tta aag gtg gac aaa gag acc aac acg gag     2748
Met Asp Gly Tyr Pro Ala Leu Lys Val Asp Lys Glu Thr Asn Thr Glu
    880                 885                 890

acc ccg gcc cca tcc ccc aca gtg gtg cga cct aag gac cgg aga gtg     2796
Thr Pro Ala Pro Ser Pro Thr Val Val Arg Pro Lys Asp Arg Arg Val
895                 900                 905                 910
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ggc acc ccg tcc cag ggg cca ttt ctt cga ggg agc acc atc atc cgc 2844
Gly Thr Pro Ser Gln Gly Pro Phe Leu Arg Gly Ser Thr Ile Ile Arg
915 920 925

tct aag acc ttc tcc cca gga ccc cag agc cag tac gtg tgc cgg ctg 2892
Ser Lys Thr Phe Ser Pro Gly Pro Gln Ser Gln Tyr Val Cys Arg Leu
930 935 940

aat cgg agt gat agt gac agc tcc act ctg tcc aaa aag cca cct ttt 2940
Asn Arg Ser Asp Ser Asp Ser Ser Thr Leu Ser Lys Lys Pro Pro Phe
945 950 955

gtt cga aac tcc ctg gag cga cgc agc gtc cgg atg aag cgg cct tcc 2988
Val Arg Asn Ser Leu Glu Arg Arg Ser Val Arg Met Lys Arg Pro Ser
960 965 970

tcg gtc aag tcg ctg cgc tcc gag cgt ctg atc cgt acc tcg ctg gac 3036
Ser Val Lys Ser Leu Arg Ser Glu Arg Leu Ile Arg Thr Ser Leu Asp
975 980 985 990

ctg gag tta gac ctg cag gcg aca aga acc tgg cac agc caa ctg acc 3084
Leu Glu Leu Asp Leu Gln Ala Thr Arg Thr Trp His Ser Gln Leu Thr
995 1000 1005

cag gag atc tcg gtg ctg aag gag ctc aag gag cag ctg gaa caa 3129
Gln Glu Ile Ser Val Leu Lys Glu Leu Lys Glu Gln Leu Glu Gln
1010 1015 1020

gcc aag agc cac ggg gag aag gag ctg cca cag tgg ttg cgt gag 3174
Ala Lys Ser His Gly Glu Lys Glu Leu Pro Gln Trp Leu Arg Glu
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gac gag cgt ttc cgc ctg ctg ctg agg atg ctg gag aag cgg cag 3219
Asp Glu Arg Phe Arg Leu Leu Leu Arg Met Leu Glu Lys Arg Gln
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atg gac cga gcg gag cac aag ggt gag ctt cag aca gac aag atg 3264
Met Asp Arg Ala Glu His Lys Gly Glu Leu Gln Thr Asp Lys Met
1055 1060 1065

atg agg gca gct gcc aag gat gtg cac agg ctc cga ggc cag agc 3309
Met Arg Ala Ala Ala Lys Asp Val His Arg Leu Arg Gly Gln Ser
1070 1075 1080

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Cys Lys Glu Pro Pro Glu Val Gln Ser Phe Arg Glu Lys Met Ala
1085 1090 1095

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Phe Phe Thr Arg Pro Arg Met Asn Ile Pro Ala Leu Ser Ala Asp
1100 1105 1110

gac gtc taatcgccag aaaagtattt cctttgttcc actgaccagg ctgtgaacat 3455
Asp Val

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aaaaacagaa caaaaacaaa acacacacac acacaaaaac agaaacaaaa aaaaccagca 3635

ttaaaataat aagattgtat agtttgtata tttaggagtg tatttttggg aaagaaaatt 3695

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gtaatcctaa taggacgtcc cgcacttgtc acagtacagc taatttttcc tagttaacat 3875

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35 40 45

Asp Cys Ile Ser Asp Glu Leu Pro Leu Gly Trp Glu Glu Ala Tyr Asp
50 55 60

Pro Gln Val Gly Asp Tyr Phe Ile Asp His Asn Thr Lys Thr Thr Gln
65 70 75 80

Ile Glu Asp Pro Arg Val Gln Trp Arg Arg Glu Gln Glu His Met Leu
85 90 95

Lys Asp Tyr Leu Val Val Ala Gln Glu Ala Leu Ser Ala Gln Lys Glu
100 105 110

Ile Tyr Gln Val Lys Gln Gln Arg Leu Glu Leu Ala Gln Gln Glu Tyr
115 120 125

Gln Gln Leu His Ala Val Trp Glu His Lys Leu Gly Ser Gln Val Ser
130 135 140

Leu Val Ser Gly Ser Ser Ser Ser Ser Lys Tyr Asp Pro Glu Ile Leu
145 150 155 160

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Lys Ala Glu Ile Ala Thr Ala Lys Ser Arg Val Asn Lys Leu Lys Arg
                165                 170                 175

Glu Met Val His Leu Gln His Glu Leu Gln Phe Lys Glu Arg Gly Phe
            180                 185                 190

Gln Thr Leu Lys Lys Ile Asp Lys Lys Met Ser Asp Ala Gln Gly Ser
        195                 200                 205

Tyr Lys Leu Asp Glu Ala Gln Ala Val Leu Arg Glu Thr Lys Ala Ile
    210                 215                 220

Lys Lys Ala Ile Thr Cys Gly Glu Lys Glu Lys Gln Asp Leu Ile Lys
225                 230                 235                 240

Ser Leu Ala Met Leu Lys Asp Gly Phe Arg Thr Asp Arg Gly Ser His
                245                 250                 255

Ser Asp Leu Trp Ser Ser Ser Ser Ser Leu Glu Ser Ser Ser Phe Pro
            260                 265                 270

Leu Pro Lys Gln Tyr Leu Asp Val Ser Ser Gln Thr Asp Ile Ser Gly
        275                 280                 285

Ser Phe Gly Ile Asn Ser Asn Asn Gln Leu Ala Glu Lys Val Arg Leu
    290                 295                 300

Arg Leu Arg Tyr Glu Glu Ala Lys Arg Arg Ile Ala Asn Leu Lys Ile
305                 310                 315                 320

Gln Leu Ala Lys Leu Asp Ser Glu Ala Trp Pro Gly Val Leu Asp Ser
                325                 330                 335

Glu Arg Asp Arg Leu Ile Leu Ile Asn Glu Lys Glu Glu Leu Leu Lys
            340                 345                 350

Glu Met Arg Phe Ile Ser Pro Arg Lys Trp Thr Gln Gly Glu Val Glu
        355                 360                 365

Gln Leu Glu Met Ala Arg Lys Arg Leu Glu Lys Asp Leu Gln Ala Ala
    370                 375                 380

Arg Asp Thr Gln Ser Lys Ala Leu Thr Glu Arg Leu Lys Leu Asn Ser
385                 390                 395                 400

Lys Arg Asn Gln Leu Val Arg Glu Leu Glu Glu Ala Thr Arg Gln Val
                405                 410                 415

Ala Thr Leu His Ser Gln Leu Lys Ser Leu Ser Ser Ser Met Gln Ser
            420                 425                 430
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Leu Ser Ser Gly Ser Ser Pro Gly Ser Leu Thr Ser Ser Arg Gly Ser
        435                 440                 445

Leu Val Ala Ser Ser Leu Asp Ser Ser Thr Ser Ala Ser Phe Thr Asp
    450                 455                 460

Leu Tyr Tyr Asp Pro Phe Glu Gln Leu Asp Ser Glu Leu Gln Ser Lys
465                 470                 475                 480

Val Glu Phe Leu Leu Leu Glu Gly Ala Thr Gly Phe Arg Pro Ser Gly
                485                 490                 495

Cys Ile Thr Thr Ile His Glu Asp Glu Val Ala Lys Thr Gln Lys Ala
            500                 505                 510

Glu Gly Gly Gly Arg Leu Gln Ala Leu Arg Ser Leu Ser Gly Thr Pro
        515                 520                 525

Lys Ser Met Thr Ser Leu Ser Pro Arg Ser Ser Leu Ser Ser Pro Ser
    530                 535                 540

Pro Pro Cys Ser Pro Leu Met Ala Asp Pro Leu Leu Ala Gly Asp Ala
545                 550                 555                 560

Phe Leu Asn Ser Leu Glu Phe Glu Asp Pro Glu Leu Ser Ala Thr Leu
                565                 570                 575

Cys Glu Leu Ser Leu Gly Asn Ser Ala Gln Glu Arg Tyr Arg Leu Glu
            580                 585                 590

Glu Pro Gly Thr Glu Gly Lys Gln Leu Gly Gln Ala Val Asn Thr Ala
        595                 600                 605

Gln Gly Cys Gly Leu Lys Val Ala Cys Val Ser Ala Ala Val Ser Asp
    610                 615                 620

Glu Ser Val Ala Gly Asp Ser Gly Val Tyr Glu Ala Ser Val Gln Arg
625                 630                 635                 640

Leu Gly Ala Ser Glu Ala Ala Ala Phe Asp Ser Asp Glu Ser Glu Ala
                645                 650                 655

Val Gly Ala Thr Arg Ile Gln Ile Ala Leu Lys Tyr Asp Glu Lys Asn
            660                 665                 670

Lys Gln Phe Ala Ile Leu Ile Ile Gln Leu Ser Asn Leu Ser Ala Leu

        675                 680                 685

Leu Gln Gln Gln Asp Gln Lys Val Asn Ile Arg Val Ala Val Leu Pro
    690                 695                 700
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Cys Ser Glu Ser Thr Thr Cys Leu Phe Arg Thr Arg Pro Leu Asp Ala
705                 710                 715                 720

Ser Asp Thr Leu Val Phe Asn Glu Val Phe Trp Val Ser Met Ser Tyr
                725                 730                 735

Pro Ala Leu His Gln Lys Thr Leu Arg Val Asp Val Cys Thr Thr Asp
            740                 745                 750

Arg Ser His Leu Glu Glu Cys Leu Gly Gly Ala Gln Ile Ser Leu Ala
        755                 760                 765

Glu Val Cys Arg Ser Gly Glu Arg Ser Thr Arg Trp Tyr Asn Leu Leu
    770                 775                 780

Ser Tyr Lys Tyr Leu Lys Lys Gln Ser Arg Glu Leu Lys Pro Val Gly
785                 790                 795                 800

Val Met Ala Pro Ala Ser Gly Pro Ala Ser Thr Asp Ala Val Ser Ala
                805                 810                 815

Leu Leu Glu Gln Thr Ala Val Glu Leu Glu Lys Arg Gln Glu Gly Arg
            820                 825                 830

Ser Ser Thr Gln Thr Leu Glu Asp Ser Trp Arg Tyr Glu Glu Thr Ser
        835                 840                 845

Glu Asn Glu Ala Val Ala Glu Glu Glu Glu Glu Glu Val Glu Glu Glu
    850                 855                 860

Glu Gly Glu Glu Asp Val Phe Thr Glu Lys Ala Ser Pro Asp Met Asp
865                 870                 875                 880

Gly Tyr Pro Ala Leu Lys Val Asp Lys Glu Thr Asn Thr Glu Thr Pro
                885                 890                 895

Ala Pro Ser Pro Thr Val Val Arg Pro Lys Asp Arg Arg Val Gly Thr
            900                 905                 910

Pro Ser Gln Gly Pro Phe Leu Arg Gly Ser Thr Ile Ile Arg Ser Lys
        915                 920                 925

Thr Phe Ser Pro Gly Pro Gln Ser Gln Tyr Val Cys Arg Leu Asn Arg
    930                 935                 940

Ser Asp Ser Asp Ser Ser Thr Leu Ser Lys Lys Pro Pro Phe Val Arg
945                 950                 955                 960

Asn Ser Leu Glu Arg Arg Ser Val Arg Met Lys Arg Pro Ser Ser Val
                965                 970                 975
```

```
Lys Ser Leu Arg Ser Glu Arg Leu Ile Arg Thr Ser Leu Asp Leu Glu
            980                 985                 990

Leu Asp Leu Gln Ala Thr Arg Thr  Trp His Ser Gln Leu  Thr Gln Glu
        995                 1000                1005

Ile Ser  Val Leu Lys Glu Leu  Lys Glu Gln Leu Glu  Gln Ala Lys
    1010                 1015                 1020

Ser His  Gly Glu Lys Glu Leu  Pro Gln Trp Leu Arg  Glu Asp Glu
    1025                 1030                 1035

Arg Phe  Arg Leu Leu Leu Arg  Met Leu Glu Lys Arg  Gln Met Asp
    1040                 1045                 1050

Arg Ala  Glu His Lys Gly Glu  Leu Gln Thr Asp Lys  Met Met Arg
    1055                 1060                 1065

Ala Ala  Ala Lys Asp Val His  Arg Leu Arg Gly Gln  Ser Cys Lys
    1070                 1075                 1080

Glu Pro  Pro Glu Val Gln Ser  Phe Arg Glu Lys Met  Ala Phe Phe
    1085                 1090                 1095

Thr Arg  Pro Arg Met Asn Ile  Pro Ala Leu Ser Ala  Asp Asp Val
    1100                 1105                 1110
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<212> DNA

<213> NM_001306 CLDN3, claudin 3

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<222> (198)..(857)

<223>

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cgcgcgccgt cggtgagtca gtccgtccgt ccgtccgtcc gtcggggcgc cgcagctccc     120

gccaggccca gcggccccgg cccctcgtct ccccgcaccc ggagccaccc ggtggagcgg     180

gccttgccgc ggcagcc atg tcc atg ggc ctg gag atc acg ggc acc gcg        230
                   Met Ser Met Gly Leu Glu Ile Thr Gly Thr Ala
```

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                    1               5                   10

ctg gcc gtg ctg ggc tgg ctg ggc acc atc gtg tgc tgc gcg ttg ccc      278
Leu Ala Val Leu Gly Trp Leu Gly Thr Ile Val Cys Cys Ala Leu Pro
            15                  20                  25

atg tgg cgc gtg tcg gcc ttc atc ggc agc aac atc atc acg tcg cag      326
Met Trp Arg Val Ser Ala Phe Ile Gly Ser Asn Ile Ile Thr Ser Gln
        30                  35                  40

aac atc tgg gag ggc ctg tgg atg aac tgc gtg gtg cag agc acc ggc      374
Asn Ile Trp Glu Gly Leu Trp Met Asn Cys Val Val Gln Ser Thr Gly
    45                  50                  55

cag atg cag tgc aag gtg tac gac tcg ctg ctg gca ctg cca cag gac      422
Gln Met Gln Cys Lys Val Tyr Asp Ser Leu Leu Ala Leu Pro Gln Asp
60                  65                  70                  75

ctt cag gcg gcc cgc gcc ctc atc gtg gtg gcc atc ctg ctg gcc gcc      470
Leu Gln Ala Ala Arg Ala Leu Ile Val Val Ala Ile Leu Leu Ala Ala
                80                  85                  90

ttc ggg ctg cta gtg gcg ctg gtg ggc gcc cag tgc acc aac tgc gtg      518
Phe Gly Leu Leu Val Ala Leu Val Gly Ala Gln Cys Thr Asn Cys Val
            95                  100                 105

cag gac gac acg gcc aag gcc aag atc acc atc gtg gca ggc gtg ctg      566
Gln Asp Asp Thr Ala Lys Ala Lys Ile Thr Ile Val Ala Gly Val Leu
        110                 115                 120

ttc ctt ctc gcc gcc ctg ctc acc ctc gtg ccg gtg tcc tgg tcg gcc      614
Phe Leu Leu Ala Ala Leu Leu Thr Leu Val Pro Val Ser Trp Ser Ala
    125                 130                 135

aac acc att atc cgg gac ttc tac aac ccc gtg gtg ccc gag gcg cag      662
Asn Thr Ile Ile Arg Asp Phe Tyr Asn Pro Val Val Pro Glu Ala Gln
140                 145                 150                 155

aag cgc gag atg ggc gcg ggc ctg tac gtg ggc tgg gcg gcc gcg gcg      710
Lys Arg Glu Met Gly Ala Gly Leu Tyr Val Gly Trp Ala Ala Ala Ala
                160                 165                 170

ctg cag ctg ctg ggg ggc gcg ctg ctc tgc tgc tcg tgt ccc cca cgc      758
Leu Gln Leu Leu Gly Gly Ala Leu Leu Cys Cys Ser Cys Pro Pro Arg
            175                 180                 185

gag aag aag tac acg gcc acc aag gtc gtc tac tcc gcg ccg cgc tcc      806
Glu Lys Lys Tyr Thr Ala Thr Lys Val Val Tyr Ser Ala Pro Arg Ser
        190                 195                 200

acc ggc ccg gga gcc agc ctg ggc aca ggc tac gac cgc aag gac tac      854
Thr Gly Pro Gly Ala Ser Leu Gly Thr Gly Tyr Asp Arg Lys Asp Tyr
    205                 210                 215

gtc taagggacag acgcagggag accccaccac caccaccacc accaacacca           907
Val
220

ccaccaccac cgcgagctgg agcgcgcacc aggccatcca gcgtgcagcc ttgcctcgga     967

ggccagccca cccccagaag ccaggaagcc cccgcgctgg actggggcag cttccccagc    1027

agccacggct ttgcgggccg ggcagtcgac ttcggggccc agggaccaac ctgcatggac    1087

tgtgaaacct caccccttctg gagcacgggg cctgggtgac cgccaatact tgaccacccc   1147

gtcgagcccc atcgggccgc tgcccccatg ctcgcgctgg gcagggaccg gcagccctgg    1207
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aaggggcact tgatattttt caataaaagc ctttcgtttt gcaaaaaaaa aaaaaaaaaa 1267

aaaaaaaaaa aaaaaaaaaa aaaaaaa 1294

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<212> PRT

<213> NM_001306 CLDN3, claudin 3

<400> 16

Met Ser Met Gly Leu Glu Ile Thr Gly Thr Ala Leu Ala Val Leu Gly
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Trp Leu Gly Thr Ile Val Cys Cys Ala Leu Pro Met Trp Arg Val Ser
20 25 30

Ala Phe Ile Gly Ser Asn Ile Ile Thr Ser Gln Asn Ile Trp Glu Gly
35 40 45

Leu Trp Met Asn Cys Val Val Gln Ser Thr Gly Gln Met Gln Cys Lys
50 55 60

Val Tyr Asp Ser Leu Leu Ala Leu Pro Gln Asp Leu Gln Ala Ala Arg
65 70 75 80

Ala Leu Ile Val Val Ala Ile Leu Leu Ala Ala Phe Gly Leu Leu Val
85 90 95

Ala Leu Val Gly Ala Gln Cys Thr Asn Cys Val Gln Asp Asp Thr Ala
100 105 110

Lys Ala Lys Ile Thr Ile Val Ala Gly Val Leu Phe Leu Leu Ala Ala
115 120 125

Leu Leu Thr Leu Val Pro Val Ser Trp Ser Ala Asn Thr Ile Ile Arg
130 135 140

Asp Phe Tyr Asn Pro Val Val Pro Glu Ala Gln Lys Arg Glu Met Gly
145 150 155 160

Ala Gly Leu Tyr Val Gly Trp Ala Ala Ala Ala Leu Gln Leu Leu Gly
165 170 175

Gly Ala Leu Leu Cys Cys Ser Cys Pro Pro Arg Glu Lys Lys Tyr Thr
180 185 190

Ala Thr Lys Val Val Tyr Ser Ala Pro Arg Ser Thr Gly Pro Gly Ala
195 200 205

Ser Leu Gly Thr Gly Tyr Asp Arg Lys Asp Tyr Val
210 215 220

<210> 17

<211> 1853

<212> DNA

<213> NM_022454 SOX17

<220>

<221> CDS

<222> (205)..(1446)

<223>

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agaacacggg cggcggcttc gggccgggag acccgcgcag ccctcggggc atctcagtgc 120

ctcactcccc accccctccc ccgggtcggg ggaggcggcg cgtccggcgg agggttgagg 180

ggagcggggc aggcctggag cgcc atg agc agc ccg gat gcg gga tac gcc 231
Met Ser Ser Pro Asp Ala Gly Tyr Ala
1 5

agt gac gac cag agc cag acc cag agc gcg ctg ccc gcg gtg atg gcc 279
Ser Asp Asp Gln Ser Gln Thr Gln Ser Ala Leu Pro Ala Val Met Ala
10 15 20 25

ggg ctg ggc ccc tgc ccc tgg gcc gag tcg ctg agc ccc atc ggg gac 327
Gly Leu Gly Pro Cys Pro Trp Ala Glu Ser Leu Ser Pro Ile Gly Asp
30 35 40

atg aag gtg aag ggc gag gcg ccg gcg aac agc gga gca ccg gcc ggg 375
Met Lys Val Lys Gly Glu Ala Pro Ala Asn Ser Gly Ala Pro Ala Gly
45 50 55

gcc gcg ggc cga gcc aag ggc gag tcc cgt atc cgg cgg ccg atg aac 423
Ala Ala Gly Arg Ala Lys Gly Glu Ser Arg Ile Arg Arg Pro Met Asn
60 65 70

gct ttc atg gtg tgg gct aag gac gag cgc aag cgg ctg gcg cag cag 471

Ala Phe Met Val Trp Ala Lys Asp Glu Arg Lys Arg Leu Ala Gln Gln
75 80 85

aat cca gac ctg cac aac gcc gag ttg agc aag atg ctg ggc aag tcg 519
Asn Pro Asp Leu His Asn Ala Glu Leu Ser Lys Met Leu Gly Lys Ser
90 95 100 105

tgg aag gcg ctg acg ctg gcg gag aag cgg ccc ttc gtg gag gag gca 567
Trp Lys Ala Leu Thr Leu Ala Glu Lys Arg Pro Phe Val Glu Glu Ala
110 115 120

gag cgg ctg cgc gtg cag cac atg cag gac cac ccc aac tac aag tac 615
Glu Arg Leu Arg Val Gln His Met Gln Asp His Pro Asn Tyr Lys Tyr
125 130 135

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cgg ccg cgg cgg cgc aag cag gtg aag cgg ctg aag cgg gtg gag ggc      663
Arg Pro Arg Arg Arg Lys Gln Val Lys Arg Leu Lys Arg Val Glu Gly
        140                 145                 150

ggc ttc ctg cac ggc ctg gct gag ccg cag gcg gcc gcg ctg ggc ccc      711
Gly Phe Leu His Gly Leu Ala Glu Pro Gln Ala Ala Ala Leu Gly Pro
    155                 160                 165

gag ggc ggc cgc gtg gcc atg gac ggc ctg ggc ctc cag ttc ccc gag      759
Glu Gly Gly Arg Val Ala Met Asp Gly Leu Gly Leu Gln Phe Pro Glu
170                 175                 180                 185

cag ggc ttc ccc gcc ggc ccg ccg ctg ctg cct ccg cac atg ggc ggc      807
Gln Gly Phe Pro Ala Gly Pro Pro Leu Leu Pro Pro His Met Gly Gly
                190                 195                 200

cac tac cgc gac tgc cag agt ctg ggc gcg cct ccg ctc gac ggc tac      855

His Tyr Arg Asp Cys Gln Ser Leu Gly Ala Pro Pro Leu Asp Gly Tyr
            205                 210                 215

ccg ttg ccc acg ccc gac acg tcc ccg ctg gac ggc gtg gac ccc gac      903
Pro Leu Pro Thr Pro Asp Thr Ser Pro Leu Asp Gly Val Asp Pro Asp
        220                 225                 230

ccg gct ttc ttc gcc gcc ccg atg ccc ggg gac tgc ccg gcg gcc ggc      951
Pro Ala Phe Phe Ala Ala Pro Met Pro Gly Asp Cys Pro Ala Ala Gly
    235                 240                 245

acc tac agc tac gcg cag gtc tcg gac tac gct ggc ccc ccg gag cct      999
Thr Tyr Ser Tyr Ala Gln Val Ser Asp Tyr Ala Gly Pro Pro Glu Pro
250                 255                 260                 265

ccc gcc ggt ccc atg cac ccc cga ctc ggc cca gag ccc gcg ggt ccc     1047
Pro Ala Gly Pro Met His Pro Arg Leu Gly Pro Glu Pro Ala Gly Pro
                270                 275                 280

tcg att ccg ggc ctc ctg gcg cca ccc agc gcc ctt cac gtg tac tac     1095
Ser Ile Pro Gly Leu Leu Ala Pro Pro Ser Ala Leu His Val Tyr Tyr
            285                 290                 295

ggc gcg atg ggc tcg ccc ggg gcg ggc ggc ggg cgc ggc ttc cag atg     1143
Gly Ala Met Gly Ser Pro Gly Ala Gly Gly Gly Arg Gly Phe Gln Met
        300                 305                 310

cag ccg caa cac cag cac cag cac cag cac cag cac cac ccc ccg ggc     1191
Gln Pro Gln His Gln His Gln His Gln His Gln His His Pro Pro Gly
    315                 320                 325

ccc gga cag ccg tcg ccc cct ccg gag gca ctg ccc tgc cgg gac ggc     1239

Pro Gly Gln Pro Ser Pro Pro Pro Glu Ala Leu Pro Cys Arg Asp Gly
330                 335                 340                 345

acg gac ccc agt cag ccc gcc gag ctc ctc ggg gag gtg gac cgc acg     1287
Thr Asp Pro Ser Gln Pro Ala Glu Leu Leu Gly Glu Val Asp Arg Thr
                350                 355                 360

gaa ttt gaa cag tat ctg cac ttc gtg tgc aag cct gag atg ggc ctc     1335
Glu Phe Glu Gln Tyr Leu His Phe Val Cys Lys Pro Glu Met Gly Leu
            365                 370                 375

ccc tac cag ggg cat gac tcc ggt gtg aat ctc ccc gac agc cac ggg     1383
Pro Tyr Gln Gly His Asp Ser Gly Val Asn Leu Pro Asp Ser His Gly
        380                 385                 390

gcc att tcc tcg gtg gtg tcc gac gcc agc tcc gcg gta tat tac tgc     1431
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Ala Ile Ser Ser Val Val Ser Asp Ala Ser Ser Ala Val Tyr Tyr Cys
    395   400   405

aac tat cct gac gtg tgacaggtcc ctgatccgcc ccagcctgca ggccagaagc   1486
Asn Tyr Pro Asp Val
410

agtgttacac acttcctgga ggagctaagg aaatcctcag actcctgggt ttttgttgtt   1546

gctgttgttg ttttttaaaa ggtgtgttgg catataattt atggtaattt attttgtctg   1606

ccacttgaac agtttggggg ggtgaggttt catttaaaat ttgttcagag atttgtttcc   1666

catagttgga ttgtcaaaac cctatttcca agttcaagtt aactagcttt gaatgtgtcc   1726

caaaacagct tcctccattt cctgaaagtt tattgatcaa agaaatgttg tcctgggtgt   1786

gtttttcaa tcttctaaaa aataaaatct ggaatcctga aaaaaaaaaa aaaaaaaaaa   1846

aaaaaaa   1853

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<212> PRT

<213> NM_022454 SOX17

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Met Ser Ser Pro Asp Ala Gly Tyr Ala Ser Asp Asp Gln Ser Gln Thr
1   5   10   15

Gln Ser Ala Leu Pro Ala Val Met Ala Gly Leu Gly Pro Cys Pro Trp
            20   25   30

Ala Glu Ser Leu Ser Pro Ile Gly Asp Met Lys Val Lys Gly Glu Ala
        35   40   45

Pro Ala Asn Ser Gly Ala Pro Ala Gly Ala Ala Gly Arg Ala Lys Gly
    50   55   60

Glu Ser Arg Ile Arg Arg Pro Met Asn Ala Phe Met Val Trp Ala Lys
65   70   75   80

Asp Glu Arg Lys Arg Leu Ala Gln Gln Asn Pro Asp Leu His Asn Ala
                85   90   95

Glu Leu Ser Lys Met Leu Gly Lys Ser Trp Lys Ala Leu Thr Leu Ala
            100   105   110

Glu Lys Arg Pro Phe Val Glu Glu Ala Glu Arg Leu Arg Val Gln His
        115   120   125

Met Gln Asp His Pro Asn Tyr Lys Tyr Arg Pro Arg Arg Arg Lys Gln
    130   135   140

Val Lys Arg Leu Lys Arg Val Glu Gly Gly Phe Leu His Gly Leu Ala
145 150 155 160

Glu Pro Gln Ala Ala Ala Leu Gly Pro Glu Gly Gly Arg Val Ala Met
165 170 175

Asp Gly Leu Gly Leu Gln Phe Pro Glu Gln Gly Phe Pro Ala Gly Pro
180 185 190

Pro Leu Leu Pro Pro His Met Gly Gly His Tyr Arg Asp Cys Gln Ser
195 200 205

Leu Gly Ala Pro Pro Leu Asp Gly Tyr Pro Leu Pro Thr Pro Asp Thr
210 215 220

Ser Pro Leu Asp Gly Val Asp Pro Asp Pro Ala Phe Phe Ala Ala Pro
225 230 235 240

Met Pro Gly Asp Cys Pro Ala Ala Gly Thr Tyr Ser Tyr Ala Gln Val
245 250 255

Ser Asp Tyr Ala Gly Pro Pro Glu Pro Pro Ala Gly Pro Met His Pro
260 265 270

Arg Leu Gly Pro Glu Pro Ala Gly Pro Ser Ile Pro Gly Leu Leu Ala
275 280 285

Pro Pro Ser Ala Leu His Val Tyr Tyr Gly Ala Met Gly Ser Pro Gly
290 295 300

Ala Gly Gly Gly Arg Gly Phe Gln Met Gln Pro Gln His Gln His Gln
305 310 315 320

His Gln His Gln His His Pro Pro Gly Pro Gly Gln Pro Ser Pro Pro
325 330 335

Pro Glu Ala Leu Pro Cys Arg Asp Gly Thr Asp Pro Ser Gln Pro Ala
340 345 350

Glu Leu Leu Gly Glu Val Asp Arg Thr Glu Phe Glu Gln Tyr Leu His
355 360 365

Phe Val Cys Lys Pro Glu Met Gly Leu Pro Tyr Gln Gly His Asp Ser
370 375 380

Gly Val Asn Leu Pro Asp Ser His Gly Ala Ile Ser Ser Val Val Ser
385 390 395 400

Asp Ala Ser Ser Ala Val Tyr Tyr Cys Asn Tyr Pro Asp Val
405 410

<210> 19

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<212> DNA

<213> NM_005682 GPR56

<220>

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<222> (159)..(2237)

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acctccacct cccgggttca agtgattctc atgcctcagc ctcccgagta gctgggatta     120

caggtggtga cttccaagag tgactccgtc ggaggaaa atg act ccc cag tcg ctg     176
                                          Met Thr Pro Gln Ser Leu
                                          1               5

ctg cag acg aca ctg ttc ctg ctg agt ctg ctc ttc ctg gtc caa ggt       224
Leu Gln Thr Thr Leu Phe Leu Leu Ser Leu Leu Phe Leu Val Gln Gly
            10                  15                  20

gcc cac ggc agg ggc cac agg gaa gac ttt cgc ttc tgc agc cag cgg       272
Ala His Gly Arg Gly His Arg Glu Asp Phe Arg Phe Cys Ser Gln Arg
        25                  30                  35

aac cag aca cac agg agc agc ctc cac tac aaa ccc aca cca gac ctg       320
Asn Gln Thr His Arg Ser Ser Leu His Tyr Lys Pro Thr Pro Asp Leu
    40                  45                  50

cgc atc tcc atc gag aac tcc gaa gag gcc ctc aca gtc cat gcc cct       368
Arg Ile Ser Ile Glu Asn Ser Glu Glu Ala Leu Thr Val His Ala Pro
55                  60                  65                  70

ttc cct gca gcc cac cct gct tcc cga tcc ttc cct gac ccc agg ggc       416
Phe Pro Ala Ala His Pro Ala Ser Arg Ser Phe Pro Asp Pro Arg Gly
                75                  80                  85

ctc tac cac ttc tgc ctc tac tgg aac cga cat gct ggg aga tta cat       464
Leu Tyr His Phe Cys Leu Tyr Trp Asn Arg His Ala Gly Arg Leu His
            90                  95                  100

ctt ctc tat ggc aag cgt gac ttc ttg ctg agt gac aaa gcc tct agc       512
Leu Leu Tyr Gly Lys Arg Asp Phe Leu Leu Ser Asp Lys Ala Ser Ser
        105                 110                 115

ctc ctc tgc ttc cag cac cag gag gag agc ctg gct cag ggc ccc ccg       560
Leu Leu Cys Phe Gln His Gln Glu Glu Ser Leu Ala Gln Gly Pro Pro
    120                 125                 130

ctg tta gcc act tct gtc acc tcc tgg tgg agc cct cag aac atc agc       608
Leu Leu Ala Thr Ser Val Thr Ser Trp Trp Ser Pro Gln Asn Ile Ser
135                 140                 145                 150

ctg ccc agt gcc gcc agc ttc acc ttc tcc ttc cac agt cct ccc cac       656
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Leu Pro Ser Ala Ala Ser Phe Thr Phe Ser Phe His Ser Pro Pro His
                155                 160                 165

acg gcc gct cac aat gcc tcg gtg gac atg tgc gag ctc aaa agg gac      704
Thr Ala Ala His Asn Ala Ser Val Asp Met Cys Glu Leu Lys Arg Asp
            170                 175                 180

ctc cag ctg ctc agc cag ttc ctg aag cat ccc cag aag gcc tca agg      752
Leu Gln Leu Leu Ser Gln Phe Leu Lys His Pro Gln Lys Ala Ser Arg
        185                 190                 195

agg ccc tcg gct gcc ccc gcc agc cag cag ttg cag agc ctg gag tcg      800
Arg Pro Ser Ala Ala Pro Ala Ser Gln Gln Leu Gln Ser Leu Glu Ser
    200                 205                 210

aaa ctg acc tct gtg aga ttc atg ggg gac atg gtg tcc ttc gag gag      848
Lys Leu Thr Ser Val Arg Phe Met Gly Asp Met Val Ser Phe Glu Glu
215                 220                 225                 230

gac cgg atc aac gcc acg gtg tgg aag ctc cag ccc aca gcc ggc ctc      896
Asp Arg Ile Asn Ala Thr Val Trp Lys Leu Gln Pro Thr Ala Gly Leu
                235                 240                 245

cag gac ctg cac atc cac tcc cgg cag gag gag gag cag agc gag atc      944
Gln Asp Leu His Ile His Ser Arg Gln Glu Glu Glu Gln Ser Glu Ile
            250                 255                 260

atg gag tac tcg gtg ctg ctg cct cga aca ctc ttc cag agg acg aaa      992
Met Glu Tyr Ser Val Leu Leu Pro Arg Thr Leu Phe Gln Arg Thr Lys
        265                 270                 275

ggc cgg agc ggg gag gct gag aag aga ctc ctc ctg gtg gac ttc agc     1040
Gly Arg Ser Gly Glu Ala Glu Lys Arg Leu Leu Leu Val Asp Phe Ser
    280                 285                 290

agc caa gcc ctg ttc cag gac aag aat tcc agc cac gtc ctg ggt gag     1088
Ser Gln Ala Leu Phe Gln Asp Lys Asn Ser Ser His Val Leu Gly Glu
295                 300                 305                 310

aag gtc ttg ggg att gtg gta cag aac acc aaa gta gcc aac ctc acg     1136
Lys Val Leu Gly Ile Val Val Gln Asn Thr Lys Val Ala Asn Leu Thr
                315                 320                 325

gag ccc gtg gtg ctc acc ttc cag cac cag cta cag ccg aag aat gtg     1184
Glu Pro Val Val Leu Thr Phe Gln His Gln Leu Gln Pro Lys Asn Val
            330                 335                 340

act ctg caa tgt gtg ttc tgg gtt gaa gac ccc aca ttg agc agc ccg     1232
Thr Leu Gln Cys Val Phe Trp Val Glu Asp Pro Thr Leu Ser Ser Pro
        345                 350                 355

ggg cat tgg agc agt gct ggg tgt gag acc gtc agg aga gaa acc caa     1280
Gly His Trp Ser Ser Ala Gly Cys Glu Thr Val Arg Arg Glu Thr Gln
    360                 365                 370

aca tcc tgc ttc tgc aac cac ttg acc tac ttt gca gtg ctg atg gtc     1328
Thr Ser Cys Phe Cys Asn His Leu Thr Tyr Phe Ala Val Leu Met Val
375                 380                 385                 390

tcc tcg gtg gag gtg gac gcc gtg cac aag cac tac ctg agc ctc ctc     1376
Ser Ser Val Glu Val Asp Ala Val His Lys His Tyr Leu Ser Leu Leu
                395                 400                 405

tcc tac gtg ggc tgt gtc gtc tct gcc ctg gcc tgc ctt gtc acc att     1424
Ser Tyr Val Gly Cys Val Val Ser Ala Leu Ala Cys Leu Val Thr Ile
            410                 415                 420

gcc gcc tac ctc tgc tcc agg gtg ccc ctg ccg tgc agg agg aaa cct     1472
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Ala Ala Tyr Leu Cys Ser Arg Val Pro Leu Pro Cys Arg Arg Lys Pro
425 430 435

cgg gac tac acc atc aag gtg cac atg aac ctg ctg ctg gcc gtc ttc 1520
Arg Asp Tyr Thr Ile Lys Val His Met Asn Leu Leu Leu Ala Val Phe
440 445 450

ctg ctg gac acg agc ttc ctg ctc agc gag ccg gtg gcc ctg aca ggc 1568
Leu Leu Asp Thr Ser Phe Leu Leu Ser Glu Pro Val Ala Leu Thr Gly
455 460 465 470

tct gag gct ggc tgc cga gcc agt gcc atc ttc ctg cac ttc tcc ctg 1616
Ser Glu Ala Gly Cys Arg Ala Ser Ala Ile Phe Leu His Phe Ser Leu
475 480 485

ctc acc tgc ctt tcc tgg atg ggc ctc gag ggg tac aac ctc tac cga 1664
Leu Thr Cys Leu Ser Trp Met Gly Leu Glu Gly Tyr Asn Leu Tyr Arg
490 495 500

ctc gtg gtg gag gtc ttt ggc acc tat gtc cct ggc tac cta ctc aag 1712
Leu Val Val Glu Val Phe Gly Thr Tyr Val Pro Gly Tyr Leu Leu Lys
505 510 515

ctg agc gcc atg ggc tgg ggc ttc ccc atc ttt ctg gtg acg ctg gtg 1760
Leu Ser Ala Met Gly Trp Gly Phe Pro Ile Phe Leu Val Thr Leu Val
520 525 530

gcc ctg gtg gat gtg gac aac tat ggc ccc atc atc ttg gct gtg cat 1808
Ala Leu Val Asp Val Asp Asn Tyr Gly Pro Ile Ile Leu Ala Val His
535 540 545 550

agg act cca gag ggc gtc atc tac cct tcc atg tgc tgg atc cgg gac 1856
Arg Thr Pro Glu Gly Val Ile Tyr Pro Ser Met Cys Trp Ile Arg Asp
555 560 565

tcc ctg gtc agc tac atc acc aac ctg ggc ctc ttc agc ctg gtg ttt 1904
Ser Leu Val Ser Tyr Ile Thr Asn Leu Gly Leu Phe Ser Leu Val Phe
570 575 580

ctg ttc aac atg gcc atg cta gcc acc atg gtg gtg cag atc ctg cgg 1952
Leu Phe Asn Met Ala Met Leu Ala Thr Met Val Val Gln Ile Leu Arg
585 590 595

ctg cgc ccc cac acc caa aag tgg tca cat gtg ctg aca ctg ctg ggc 2000
Leu Arg Pro His Thr Gln Lys Trp Ser His Val Leu Thr Leu Leu Gly
600 605 610

ctc agc ctg gtc ctt ggc ctg ccc tgg gcc ttg atc ttc ttc tcc ttt 2048
Leu Ser Leu Val Leu Gly Leu Pro Trp Ala Leu Ile Phe Phe Ser Phe
615 620 625 630

gct tct ggc acc ttc cag ctt gtc gtc ctc tac ctt ttc agc atc atc 2096
Ala Ser Gly Thr Phe Gln Leu Val Val Leu Tyr Leu Phe Ser Ile Ile
635 640 645

acc tcc ttc caa ggc ttc ctc atc ttc atc tgg tac tgg tcc atg cgg 2144
Thr Ser Phe Gln Gly Phe Leu Ile Phe Ile Trp Tyr Trp Ser Met Arg
650 655 660

ctg cag gcc cgg ggt ggc ccc tcc cct ctg aag agc aac tca gac agc 2192
Leu Gln Ala Arg Gly Gly Pro Ser Pro Leu Lys Ser Asn Ser Asp Ser
665 670 675

gcc agg ctc ccc atc agc tcg ggc agc acc tcg tcc agc cgc atc 2237
Ala Arg Leu Pro Ile Ser Ser Gly Ser Thr Ser Ser Ser Arg Ile
680 685 690

taggcctcca gcccacctgc ccatgtgatg aagcagagat gcggcctcgt cgcacactgc 2297

ctgtggcccc cgagccaggc ccagccccag gccagtcagc cgcagacttt ggaaagccca 2357

acgaccatgg agagatgggc cgttgccatg gtggacggac tcccgggctg ggcttttgaa 2417

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agctgcctgg tgtctgctgt aaatgtttgt ctactgcaca agcctcggcc tgcccctgag 3017

ccaggctcgg taccgatgcg tgggctgggc taggtccctc tgtccatctg ggcctttgta 3077

tgagctgcat tgcccttgct caccctgacc aagcacacgc ctcagagggg ccctcagcct 3137

ctcctgaagc cctcttgtgg caagaactgt ggaccatgcc agtcccgtct ggtttccatc 3197

ccaccactcc aaggactgag actgacctcc tctggtgaca ctggcctaga gcctgacact 3257

ctcctaagag gttctctcca agcccccaaa tagctccagg cgccctcggc cgcccatcat 3317

ggttaattct gtccaacaaa cacacacggg tagattgctg gcctgttgta ggtggtaggg 3377

acacagatga ccgacctggt cactcctcct gccaacattc agtctggtat gtgaggcgtg 3437

cgtgaagcaa gaactcctgg agctacaggg acagggagcc atcattcctg cctgggaatc 3497

ctggaagact tcctgcagga gtcagcgttc aatcttgacc ttgaagatgg gaaggatgtt 3557

ctttttacgt accaattctt ttgtcttttg atattaaaaa gaagtacatg ttcattgtag 3617

agaatttgga aactgtagaa gagaatcaag aagaaaaata aaaatcagct gttgtaatcg 3677

cctagcaaaa aaaaaaaaaa aaaaa 3702

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<211> 693

<212> PRT

<213> NM_005682 GPR56

<400> 20

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20 25 30

Arg Phe Cys Ser Gln Arg Asn Gln Thr His Arg Ser Ser Leu His Tyr
35 40 45

Lys Pro Thr Pro Asp Leu Arg Ile Ser Ile Glu Asn Ser Glu Glu Ala
50 55 60

Leu Thr Val His Ala Pro Phe Pro Ala Ala His Pro Ala Ser Arg Ser
65 70 75 80

Phe Pro Asp Pro Arg Gly Leu Tyr His Phe Cys Leu Tyr Trp Asn Arg
85 90 95

His Ala Gly Arg Leu His Leu Leu Tyr Gly Lys Arg Asp Phe Leu Leu
100 105 110

Ser Asp Lys Ala Ser Ser Leu Leu Cys Phe Gln His Gln Glu Glu Ser
115 120 125

Leu Ala Gln Gly Pro Pro Leu Leu Ala Thr Ser Val Thr Ser Trp Trp
130 135 140

Ser Pro Gln Asn Ile Ser Leu Pro Ser Ala Ala Ser Phe Thr Phe Ser
145 150 155 160

Phe His Ser Pro Pro His Thr Ala Ala His Asn Ala Ser Val Asp Met
165 170 175

Cys Glu Leu Lys Arg Asp Leu Gln Leu Leu Ser Gln Phe Leu Lys His
180 185 190

Pro Gln Lys Ala Ser Arg Arg Pro Ser Ala Ala Pro Ala Ser Gln Gln
195 200 205

Leu Gln Ser Leu Glu Ser Lys Leu Thr Ser Val Arg Phe Met Gly Asp
210 215 220

Met Val Ser Phe Glu Glu Asp Arg Ile Asn Ala Thr Val Trp Lys Leu
225 230 235 240

Gln Pro Thr Ala Gly Leu Gln Asp Leu His Ile His Ser Arg Gln Glu
245 250 255

Glu Glu Gln Ser Glu Ile Met Glu Tyr Ser Val Leu Leu Pro Arg Thr
260 265 270

Leu Phe Gln Arg Thr Lys Gly Arg Ser Gly Glu Ala Glu Lys Arg Leu
275 280 285

Leu Leu Val Asp Phe Ser Ser Gln Ala Leu Phe Gln Asp Lys Asn Ser

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290                 295                 300

Ser His Val Leu Gly Glu Lys Val Leu Gly Ile Val Val Gln Asn Thr
305                 310                 315                 320

Lys Val Ala Asn Leu Thr Glu Pro Val Val Leu Thr Phe Gln His Gln
                325                 330                 335

Leu Gln Pro Lys Asn Val Thr Leu Gln Cys Val Phe Trp Val Glu Asp
            340                 345                 350

Pro Thr Leu Ser Ser Pro Gly His Trp Ser Ser Ala Gly Cys Glu Thr
        355                 360                 365

Val Arg Arg Glu Thr Gln Thr Ser Cys Phe Cys Asn His Leu Thr Tyr
    370                 375                 380

Phe Ala Val Leu Met Val Ser Ser Val Glu Val Asp Ala Val His Lys
385                 390                 395                 400

His Tyr Leu Ser Leu Leu Ser Tyr Val Gly Cys Val Val Ser Ala Leu
                405                 410                 415

Ala Cys Leu Val Thr Ile Ala Ala Tyr Leu Cys Ser Arg Val Pro Leu
            420                 425                 430

Pro Cys Arg Arg Lys Pro Arg Asp Tyr Thr Ile Lys Val His Met Asn
        435                 440                 445

Leu Leu Leu Ala Val Phe Leu Leu Asp Thr Ser Phe Leu Leu Ser Glu
    450                 455                 460

Pro Val Ala Leu Thr Gly Ser Glu Ala Gly Cys Arg Ala Ser Ala Ile
465                 470                 475                 480

Phe Leu His Phe Ser Leu Leu Thr Cys Leu Ser Trp Met Gly Leu Glu
                485                 490                 495

Gly Tyr Asn Leu Tyr Arg Leu Val Val Glu Val Phe Gly Thr Tyr Val
            500                 505                 510

Pro Gly Tyr Leu Leu Lys Leu Ser Ala Met Gly Trp Gly Phe Pro Ile
        515                 520                 525

Phe Leu Val Thr Leu Val Ala Leu Val Asp Val Asp Asn Tyr Gly Pro
    530                 535                 540

Ile Ile Leu Ala Val His Arg Thr Pro Glu Gly Val Ile Tyr Pro Ser
545                 550                 555                 560
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Met Cys Trp Ile Arg Asp Ser Leu Val Ser Tyr Ile Thr Asn Leu Gly
565 570 575

Leu Phe Ser Leu Val Phe Leu Phe Asn Met Ala Met Leu Ala Thr Met
580 585 590

Val Val Gln Ile Leu Arg Leu Arg Pro His Thr Gln Lys Trp Ser His
595 600 605

Val Leu Thr Leu Leu Gly Leu Ser Leu Val Leu Gly Leu Pro Trp Ala
610 615 620

Leu Ile Phe Phe Ser Phe Ala Ser Gly Thr Phe Gln Leu Val Val Leu
625 630 635 640

Tyr Leu Phe Ser Ile Ile Thr Ser Phe Gln Gly Phe Leu Ile Phe Ile
645 650 655

Trp Tyr Trp Ser Met Arg Leu Gln Ala Arg Gly Gly Pro Ser Pro Leu
660 665 670

Lys Ser Asn Ser Asp Ser Ala Arg Leu Pro Ile Ser Ser Gly Ser Thr
675 680 685

Ser Ser Ser Arg Ile
690

<210> 21

<211> 1332

<212> DNA

<213> NM_001307 claudin 7, CLDN7

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<221> CDS

<222> (427)..(1059)

<223>

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gatactttgg gacttgccgg cgctcagaaa cgcgcccaga cggcccctcc accttttgtt 120

tgcctagggt cgccgagagc gcccggaggg aaccgcctgg ccttcgggga ccaccaattt 180

tgtctggaac caccctcccg gcgtatccta ctccctgtgc cgcgaggcca tcgcttcact 240

ggaggggtcg atttgtgtgt agtttggtga caagatttgc attcacctgg cccaaaccct 300

ttttgtctct ttgggtgacc ggaaaactcc acctcaagtt ttcttttgtg gggctgcccc 360

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ccaagtgtcg tttgttttac tgtagggtct cccgccccggc gcccccagtg ttttctgagg     420

gcggaa atg gcc aat tcg ggc ctg cag ttg ctg ggc ttc tcc atg gcc         468
       Met Ala Asn Ser Gly Leu Gln Leu Leu Gly Phe Ser Met Ala
       1               5                   10

ctg ctg ggc tgg gtg ggt ctg gtg gcc tgc acc gcc atc ccg cag tgg        516
Leu Leu Gly Trp Val Gly Leu Val Ala Cys Thr Ala Ile Pro Gln Trp
15                  20                  25                  30

cag atg agc tcc tat gcg ggt gac aac atc atc acg gcc cag gcc atg        564
Gln Met Ser Ser Tyr Ala Gly Asp Asn Ile Ile Thr Ala Gln Ala Met
                35                  40                  45

tac aag ggg ctg tgg atg gac tgc gtc acg cag agc acg ggg atg atg        612
Tyr Lys Gly Leu Trp Met Asp Cys Val Thr Gln Ser Thr Gly Met Met
            50                  55                  60

agc tgc aaa atg tac gac tcg gtg ctc gcc ctg tcc gcg gcc ttg cag        660
Ser Cys Lys Met Tyr Asp Ser Val Leu Ala Leu Ser Ala Ala Leu Gln
    65                  70                  75

gcc act cga gcc cta atg gtg gtc tcc ctg gtg ctg ggc ttc ctg gcc        708
Ala Thr Arg Ala Leu Met Val Val Ser Leu Val Leu Gly Phe Leu Ala
    80                  85                  90

atg ttt gtg gcc acg atg ggc atg aag tgc acg cgc tgt ggg gga gac        756
Met Phe Val Ala Thr Met Gly Met Lys Cys Thr Arg Cys Gly Gly Asp
95                  100                 105                 110

gac aaa gtg aag aag gcc cgt ata gcc atg ggt gga ggc ata att ttc        804
Asp Lys Val Lys Lys Ala Arg Ile Ala Met Gly Gly Gly Ile Ile Phe
                115                 120                 125

atc gtg gca ggt ctt gcc acc ttg gta gct tgc tcc tgg tat ggc cat        852
Ile Val Ala Gly Leu Ala Thr Leu Val Ala Cys Ser Trp Tyr Gly His
            130                 135                 140

cag att gtc aca gac ttt tat aac cct ttg atc cct acc aac att aag        900
Gln Ile Val Thr Asp Phe Tyr Asn Pro Leu Ile Pro Thr Asn Ile Lys
        145                 150                 155

tat gag ttt ggc cct gcc atc ttt att ggc tgg gca ggg tct gcc cta        948
Tyr Glu Phe Gly Pro Ala Ile Phe Ile Gly Trp Ala Gly Ser Ala Leu
    160                 165                 170

gtc atc ctg gga ggt gca ctg ctc tcc tgt tcc tgt cct ggg aat gag        996
Val Ile Leu Gly Gly Ala Leu Leu Ser Cys Ser Cys Pro Gly Asn Glu
175                 180                 185                 190

agc aag gct ggg tac cgt gca ccc cgc tct tac cct aag tcc aac tct        1044
Ser Lys Ala Gly Tyr Arg Ala Pro Arg Ser Tyr Pro Lys Ser Asn Ser
                195                 200                 205

tcc aag gag tat gtg tgacctggga tctccttgcc ccagcctgac aggctatggg        1099
Ser Lys Glu Tyr Val
            210

agtgtctaga tgcctgaaag ggcctggggc tgagctcagc ctgtgggcag ggtgccggac     1159

aaaggcctcc tggtcactct gtccctgcac tccatgtata gtcctcttgg gttgggggtg     1219

ggggggtgcc gttggtggga gagacaaaaa gagggagagt gtgcttttg tacagtaata      1279

aaaaataagt attgggaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaa           1332
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<210> 22

<211> 211

<212> PRT

<213> NM_001307 claudin 7, CLDN7

<400> 22

Met Ala Asn Ser Gly Leu Gln Leu Leu Gly Phe Ser Met Ala Leu Leu
1 5 10 15

Gly Trp Val Gly Leu Val Ala Cys Thr Ala Ile Pro Gln Trp Gln Met
20 25 30

Ser Ser Tyr Ala Gly Asp Asn Ile Ile Thr Ala Gln Ala Met Tyr Lys
35 40 45

Gly Leu Trp Met Asp Cys Val Thr Gln Ser Thr Gly Met Met Ser Cys
50 55 60

Lys Met Tyr Asp Ser Val Leu Ala Leu Ser Ala Ala Leu Gln Ala Thr
65 70 75 80

Arg Ala Leu Met Val Val Ser Leu Val Leu Gly Phe Leu Ala Met Phe
85 90 95

Val Ala Thr Met Gly Met Lys Cys Thr Arg Cys Gly Gly Asp Asp Lys
100 105 110

Val Lys Lys Ala Arg Ile Ala Met Gly Gly Gly Ile Ile Phe Ile Val
115 120 125

Ala Gly Leu Ala Thr Leu Val Ala Cys Ser Trp Tyr Gly His Gln Ile
130 135 140

Val Thr Asp Phe Tyr Asn Pro Leu Ile Pro Thr Asn Ile Lys Tyr Glu
145 150 155 160

Phe Gly Pro Ala Ile Phe Ile Gly Trp Ala Gly Ser Ala Leu Val Ile
165 170 175

Leu Gly Gly Ala Leu Leu Ser Cys Ser Cys Pro Gly Asn Glu Ser Lys
180 185 190

Ala Gly Tyr Arg Ala Pro Arg Ser Tyr Pro Lys Ser Asn Ser Ser Lys
195 200 205

Glu Tyr Val
210

<210> 23

<211> 888

<212> DNA

<213> NM_014736 KIAA0101 gene product

<220>

<221> CDS

<222> (75)..(407)

<223>

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cttcttgttt gaac atg gtg cgg act aaa gca gac agt gtt cca ggc act 110
Met Val Arg Thr Lys Ala Asp Ser Val Pro Gly Thr
1 5 10

tac aga aaa gtg gtg gct gct cga gcc ccc aga aag gtg ctt ggt tct 158
Tyr Arg Lys Val Val Ala Ala Arg Ala Pro Arg Lys Val Leu Gly Ser
15 20 25

tcc acc tct gcc act aat tcg aca tca gtt tca tcg agg aaa gct gaa 206
Ser Thr Ser Ala Thr Asn Ser Thr Ser Val Ser Ser Arg Lys Ala Glu
30 35 40

aat aaa tat gca gga ggg aac ccc gtt tgc gtg cgc cca act ccc aag 254
Asn Lys Tyr Ala Gly Gly Asn Pro Val Cys Val Arg Pro Thr Pro Lys
45 50 55 60

tgg caa aaa gga att gga gaa ttc ttt agg ttg tcc cct aaa gat tct 302
Trp Gln Lys Gly Ile Gly Glu Phe Phe Arg Leu Ser Pro Lys Asp Ser
65 70 75

gaa aaa gag aat cag att cct gaa gag gca gga agc agt ggc tta gga 350
Glu Lys Glu Asn Gln Ile Pro Glu Glu Ala Gly Ser Ser Gly Leu Gly
80 85 90

aaa gca aag aga aaa gca tgt cct ttg caa cct gat cac aca aat gat 398
Lys Ala Lys Arg Lys Ala Cys Pro Leu Gln Pro Asp His Thr Asn Asp
95 100 105

gaa aaa gaa tagaactttc tcattcatct ttgaataacg tctccttgtt 447
Glu Lys Glu
110

taccctggta ttctagaatg taaatttaca taaatgtgtt tgttccaatt agctttgttg 507

aacaggcatt taattaaaaa atttaggttt aaatttagat gttcaaaagt agttgtgaaa 567

tttgagaatt tgtaagacta attatggtaa cttagcttag tattcaatat aatgcattgt 627

ttggtttctt ttaccaaatt aagtgtctag ttcttgctaa aatcaagtca ttgcattgtg 687

ttctaattac aagtatgttg tatttgagat ttgcttagat tgttgtactg ctgccatttt 747

tattggtgtt tgattattgg aatggtgcca tattgtcact ccttctactt gctttaaaaa 807

gcagagttag atttttgcac attaaaaaaa ttcagtatta attaaacact aaaaaaaaaa 867

aaaaaaaaaa aaaaaaaaaa a 888

<210> 24

<211> 111

<212> PRT

<213> NM_014736 KIAA0101 gene product

<400> 24

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Val Ala Ala Arg Ala Pro Arg Lys Val Leu Gly Ser Ser Thr Ser Ala
20 25 30

Thr Asn Ser Thr Ser Val Ser Ser Arg Lys Ala Glu Asn Lys Tyr Ala
35 40 45

Gly Gly Asn Pro Val Cys Val Arg Pro Thr Pro Lys Trp Gln Lys Gly
50 55 60

Ile Gly Glu Phe Phe Arg Leu Ser Pro Lys Asp Ser Glu Lys Glu Asn
65 70 75 80

Gln Ile Pro Glu Glu Ala Gly Ser Ser Gly Leu Gly Lys Ala Lys Arg
85 90 95

Lys Ala Cys Pro Leu Gln Pro Asp His Thr Asn Asp Glu Lys Glu
100 105 110

<210> 25

<211> 598

<212> DNA

<213> NM_003064 secretory leukocyte protease inhibitor, SLPI

<220>

<221> CDS

<222> (23)..(418)

<223>

<400> 25
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Met Lys Ser Ser Gly Leu Phe Pro Phe Leu
1 5 10

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gtg ctg ctt gcc ctg gga act ctg gca cct tgg gct gtg gaa ggc tct      100
Val Leu Leu Ala Leu Gly Thr Leu Ala Pro Trp Ala Val Glu Gly Ser
                15                  20                  25

gga aag tcc ttc aaa gct gga gtc tgt cct cct aag aaa tct gcc cag      148
Gly Lys Ser Phe Lys Ala Gly Val Cys Pro Pro Lys Lys Ser Ala Gln
            30                  35                  40

tgc ctt aga tac aag aaa cct gag tgc cag agt gac tgg cag tgt cca      196
Cys Leu Arg Tyr Lys Lys Pro Glu Cys Gln Ser Asp Trp Gln Cys Pro
        45                  50                  55

ggg aag aag aga tgt tgt cct gac act tgt ggc atc aaa tgc ctg gat      244
Gly Lys Lys Arg Cys Cys Pro Asp Thr Cys Gly Ile Lys Cys Leu Asp
    60                  65                  70

cct gtt gac acc cca aac cca aca agg agg aag cct ggg aag tgc cca      292
Pro Val Asp Thr Pro Asn Pro Thr Arg Arg Lys Pro Gly Lys Cys Pro
75                  80                  85                  90

gtg act tat ggc caa tgt ttg atg ctt aac ccc ccc aat ttc tgt gag      340
Val Thr Tyr Gly Gln Cys Leu Met Leu Asn Pro Pro Asn Phe Cys Glu
                95                  100                 105

atg gat ggc cag tgc aag cgt gac ttg aag tgt tgc atg ggc atg tgt      388
Met Asp Gly Gln Cys Lys Arg Asp Leu Lys Cys Cys Met Gly Met Cys
            110                 115                 120

ggg aaa tcc tgc gtt tcc cct gtg aaa gct tgattcctgc catatggagg        438
Gly Lys Ser Cys Val Ser Pro Val Lys Ala
        125                 130

aggctctgga gtcctgctct gtgtggtcca ggtcctttcc accctgagac ttggctccac    498

cactgatatc ctcctttggg gaaaggcttg gcacacagca ggctttcaag aagtgccagt    558

tgatcaatga ataaataaac gagcctattt ctctttgcac                          598
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<210> 26

<211> 132

<212> PRT

<213> NM_003064 secretory leukocyte protease inhibitor, SLPI

<400> 26

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Met Lys Ser Ser Gly Leu Phe Pro Phe Leu Val Leu Leu Ala Leu Gly
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Thr Leu Ala Pro Trp Ala Val Glu Gly Ser Gly Lys Ser Phe Lys Ala
            20                  25                  30

Gly Val Cys Pro Pro Lys Lys Ser Ala Gln Cys Leu Arg Tyr Lys Lys
        35                  40                  45

Pro Glu Cys Gln Ser Asp Trp Gln Cys Pro Gly Lys Lys Arg Cys Cys
    50                  55                  60
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Pro Asp Thr Cys Gly Ile Lys Cys Leu Asp Pro Val Asp Thr Pro Asn
65 70 75 80

Pro Thr Arg Arg Lys Pro Gly Lys Cys Pro Val Thr Tyr Gly Gln Cys
85 90 95

Leu Met Leu Asn Pro Pro Asn Phe Cys Glu Met Asp Gly Gln Cys Lys
100 105 110

Arg Asp Leu Lys Cys Cys Met Gly Met Cys Gly Lys Ser Cys Val Ser
115 120 125

Pro Val Lys Ala
130

<210> 27

<211> 3970

<212> DNA

<213> NM_013994 DDR1

<220>

<221> CDS

<222> (337)..(3093)

<223>

<400> 27
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tagtatctac cttatgaagt gactgtgaag ataaaattat ggattctgtt taagggttta 120

ggccagtgtc tggcacaggg gaagcattct aaaaatatag ctgatgctgt taaacaatga 180

ctgttgttgt tgttttactg ttattatccc caaagcggcc cattctgtct gttgctgtca 240

gctatgactc agtcccctga ttaacttacg caccacccat tttatcccct gcagagatgc 300

tgcccccacc cccttaggcc cgagggatca ggagct atg gga cca gag gcc ctg 354
Met Gly Pro Glu Ala Leu
1 5

tca tct tta ctg ctg ctg ctc ttg gtg gca agt gga gat gct gac atg 402
Ser Ser Leu Leu Leu Leu Leu Leu Val Ala Ser Gly Asp Ala Asp Met
10 15 20

aag gga cat ttt gat cct gcc aag tgc cgc tat gcc ctg ggc atg cag 450
Lys Gly His Phe Asp Pro Ala Lys Cys Arg Tyr Ala Leu Gly Met Gln
25 30 35

gac cgg acc atc cca gac agt gac atc tct gct tcc agc tcc tgg tca 498
Asp Arg Thr Ile Pro Asp Ser Asp Ile Ser Ala Ser Ser Ser Trp Ser
40 45 50

gat tcc act gcc gcc cgc cac agc agg ttg gag agc agt gac ggg gat 546

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Asp Ser Thr Ala Ala Arg His Ser Arg Leu Glu Ser Ser Asp Gly Asp
55                  60                  65                  70

ggg gcc tgg tgc ccc gca ggg tcg gtg ttt ccc aag gag gag gag tac      594
Gly Ala Trp Cys Pro Ala Gly Ser Val Phe Pro Lys Glu Glu Glu Tyr
                75                  80                  85

ttg cag gtg gat cta caa cga ctg cac ctg gtg gct ctg gtg ggc acc      642
Leu Gln Val Asp Leu Gln Arg Leu His Leu Val Ala Leu Val Gly Thr
            90                  95                  100

cag gga cgg cat gcc ggg ggc ctg ggc aag gag ttc tcc cgg agc tac      690
Gln Gly Arg His Ala Gly Gly Leu Gly Lys Glu Phe Ser Arg Ser Tyr
        105                 110                 115

cgg ctg cgt tac tcc cgg gat ggt cgc cgc tgg atg ggc tgg aag gac      738
Arg Leu Arg Tyr Ser Arg Asp Gly Arg Arg Trp Met Gly Trp Lys Asp
    120                 125                 130

cgc tgg ggt cag gag gtg atc tca ggc aat gag gac cct gag gga gtg      786
Arg Trp Gly Gln Glu Val Ile Ser Gly Asn Glu Asp Pro Glu Gly Val
135                 140                 145                 150

gtg ctg aag gac ctt ggg ccc ccc atg gtt gcc cga ctg gtt cgc ttc      834
Val Leu Lys Asp Leu Gly Pro Pro Met Val Ala Arg Leu Val Arg Phe
                155                 160                 165

tac ccc cgg gct gac cgg gtc atg agc gtc tgt ctg cgg gta gag ctc      882
Tyr Pro Arg Ala Asp Arg Val Met Ser Val Cys Leu Arg Val Glu Leu
            170                 175                 180

tat ggc tgc ctc tgg agg gat gga ctc ctg tct tac acc gcc cct gtg      930
Tyr Gly Cys Leu Trp Arg Asp Gly Leu Leu Ser Tyr Thr Ala Pro Val
        185                 190                 195

ggg cag aca atg tat tta tct gag gcc gtg tac ctc aac gac tcc acc      978
Gly Gln Thr Met Tyr Leu Ser Glu Ala Val Tyr Leu Asn Asp Ser Thr
    200                 205                 210

tat gac gga cat acc gtg ggc gga ctg cag tat ggg ggt ctg ggc cag     1026
Tyr Asp Gly His Thr Val Gly Gly Leu Gln Tyr Gly Gly Leu Gly Gln
215                 220                 225                 230

ctg gca gat ggt gtg gtg ggg ctg gat gac ttt agg aag agt cag gag     1074
Leu Ala Asp Gly Val Val Gly Leu Asp Asp Phe Arg Lys Ser Gln Glu
                235                 240                 245

ctg cgg gtc tgg cca ggc tat gac tat gtg gga tgg agc aac cac agc     1122
Leu Arg Val Trp Pro Gly Tyr Asp Tyr Val Gly Trp Ser Asn His Ser
            250                 255                 260

ttc tcc agt ggc tat gtg gag atg gag ttt gag ttt gac cgg ctg agg     1170
Phe Ser Ser Gly Tyr Val Glu Met Glu Phe Glu Phe Asp Arg Leu Arg
        265                 270                 275

gcc ttc cag gct atg cag gtc cac tgt aac aac atg cac acg ctg gga     1218
Ala Phe Gln Ala Met Gln Val His Cys Asn Asn Met His Thr Leu Gly
    280                 285                 290

gcc cgt ctg cct ggc ggg gtg gaa tgt cgc ttc cgg cgt ggc cct gcc     1266
Ala Arg Leu Pro Gly Gly Val Glu Cys Arg Phe Arg Arg Gly Pro Ala
295                 300                 305                 310

atg gcc tgg gag ggg gag ccc atg cgc cac aac cta ggg ggc aac ctg     1314
Met Ala Trp Glu Gly Glu Pro Met Arg His Asn Leu Gly Gly Asn Leu
                315                 320                 325
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ggg gac ccc aga gcc cgg gct gtc tca gtg ccc ctt ggc ggc cgt gtg     1362
Gly Asp Pro Arg Ala Arg Ala Val Ser Val Pro Leu Gly Gly Arg Val
            330                 335                 340

gct cgc ttt ctg cag tgc cgc ttc ctc ttt gcg ggg ccc tgg tta ctc     1410
Ala Arg Phe Leu Gln Cys Arg Phe Leu Phe Ala Gly Pro Trp Leu Leu
        345                 350                 355

ttc agc gaa atc tcc ttc atc tct gat gtg gtg aac aat tcc tct ccg     1458
Phe Ser Glu Ile Ser Phe Ile Ser Asp Val Val Asn Asn Ser Ser Pro
    360                 365                 370

gca ctg gga ggc acc ttc ccg cca gcc ccc tgg tgg ccg cct ggc cca     1506
Ala Leu Gly Gly Thr Phe Pro Pro Ala Pro Trp Trp Pro Pro Gly Pro
375                 380                 385                 390

cct ccc acc aac ttc agc agc ttg gag ctg gag ccc aga ggc cag cag     1554
Pro Pro Thr Asn Phe Ser Ser Leu Glu Leu Glu Pro Arg Gly Gln Gln
                395                 400                 405

ccc gtg gcc aag gcc gag ggg agc ccg acc gcc atc ctc atc ggc tgc     1602
Pro Val Ala Lys Ala Glu Gly Ser Pro Thr Ala Ile Leu Ile Gly Cys
            410                 415                 420

ctg gtg gcc atc atc ctg ctc ctg ctg ctc atc att gcc ctc atg ctc     1650
Leu Val Ala Ile Ile Leu Leu Leu Leu Leu Ile Ile Ala Leu Met Leu
        425                 430                 435

tgg cgg ctg cac tgg cgc agg ctc ctc agc aag gct gaa cgg agg gtg     1698
Trp Arg Leu His Trp Arg Arg Leu Leu Ser Lys Ala Glu Arg Arg Val
    440                 445                 450

ttg gaa gag gag ctg acg gtt cac ctc tct gtc cct ggg gac act atc     1746
Leu Glu Glu Glu Leu Thr Val His Leu Ser Val Pro Gly Asp Thr Ile
455                 460                 465                 470

ctc atc aac aac cgc cca ggt cct aga gag cca ccc ccg tac cag gag     1794
Leu Ile Asn Asn Arg Pro Gly Pro Arg Glu Pro Pro Pro Tyr Gln Glu
                475                 480                 485

ccc cgg cct cgt ggg aat ccg ccc cac tcc gct ccc tgt gtc ccc aat     1842
Pro Arg Pro Arg Gly Asn Pro Pro His Ser Ala Pro Cys Val Pro Asn
            490                 495                 500

ggc tct gcg ttg ctg ctc tcc aat cca gcc tac cgc ctc ctt ctg gcc     1890
Gly Ser Ala Leu Leu Leu Ser Asn Pro Ala Tyr Arg Leu Leu Leu Ala
        505                 510                 515

act tac gcc cgt ccc cct cga ggc ccg ggc ccc ccc aca ccc gcc tgg     1938
Thr Tyr Ala Arg Pro Pro Arg Gly Pro Gly Pro Pro Thr Pro Ala Trp
    520                 525                 530

gcc aaa ccc acc aac acc cag gcc tac agt ggg gac tat atg gag cct     1986
Ala Lys Pro Thr Asn Thr Gln Ala Tyr Ser Gly Asp Tyr Met Glu Pro
535                 540                 545                 550

gag aag cca ggc gcc ccg ctt ctg ccc cca cct ccc cag aac agc gtc     2034
Glu Lys Pro Gly Ala Pro Leu Leu Pro Pro Pro Pro Gln Asn Ser Val
                555                 560                 565

ccc cat tat gcc gag gct gac att gtt acc ctg cag ggc gtc acc ggg     2082
Pro His Tyr Ala Glu Ala Asp Ile Val Thr Leu Gln Gly Val Thr Gly
            570                 575                 580
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ggc aac acc tat gct gtg cct gca ctg ccc cca ggg gca gtc ggg gat      2130
Gly Asn Thr Tyr Ala Val Pro Ala Leu Pro Pro Gly Ala Val Gly Asp
        585                 590                 595

ggg ccc ccc aga gtg gat ttc cct cga tct cga ctc cgc ttc aag gag      2178
Gly Pro Pro Arg Val Asp Phe Pro Arg Ser Arg Leu Arg Phe Lys Glu
    600                 605                 610

aag ctt ggc gag ggc cag ttt ggg gag gtg cac ctg tgt gag gtc gac      2226
Lys Leu Gly Glu Gly Gln Phe Gly Glu Val His Leu Cys Glu Val Asp
615                 620                 625                 630

agc cct caa gat ctg gtt agt ctt gat ttc ccc ctt aat gtg cgt aag      2274
Ser Pro Gln Asp Leu Val Ser Leu Asp Phe Pro Leu Asn Val Arg Lys
                635                 640                 645

gga cac cct ttg ctg gta gct gtc aag atc tta cgg cca gat gcc acc      2322
Gly His Pro Leu Leu Val Ala Val Lys Ile Leu Arg Pro Asp Ala Thr
            650                 655                 660

aag aat gcc agc ttc tcc ttg ttc tcc agg aat gat ttc ctg aaa gag      2370
Lys Asn Ala Ser Phe Ser Leu Phe Ser Arg Asn Asp Phe Leu Lys Glu
        665                 670                 675

gtg aag atc atg tcg agg ctc aag gac cca aac atc att cgg ctg ctg      2418
Val Lys Ile Met Ser Arg Leu Lys Asp Pro Asn Ile Ile Arg Leu Leu
    680                 685                 690

ggc gtg tgt gtg cag gac gac ccc ctc tgc atg att act gac tac atg      2466
Gly Val Cys Val Gln Asp Asp Pro Leu Cys Met Ile Thr Asp Tyr Met
695                 700                 705                 710

gag aac ggc gac ctc aac cag ttc ctc agt gcc cac cag ctg gag gac      2514
Glu Asn Gly Asp Leu Asn Gln Phe Leu Ser Ala His Gln Leu Glu Asp
                715                 720                 725

aag gca gcc gag ggg gcc cct ggg gac ggg cag gct gcg cag ggg ccc      2562
Lys Ala Ala Glu Gly Ala Pro Gly Asp Gly Gln Ala Ala Gln Gly Pro
            730                 735                 740

acc atc agc tac cca atg ctg ctg cat gtg gca gcc cag atc gcc tcc      2610
Thr Ile Ser Tyr Pro Met Leu Leu His Val Ala Ala Gln Ile Ala Ser
        745                 750                 755

ggc atg cgc tat ctg gcc aca ctc aac ttt gta cat cgg gac ctg gcc      2658
Gly Met Arg Tyr Leu Ala Thr Leu Asn Phe Val His Arg Asp Leu Ala
    760                 765                 770

acg cgg aac tgc cta gtt ggg gaa aat ttc acc atc aaa atc gca gac      2706
Thr Arg Asn Cys Leu Val Gly Glu Asn Phe Thr Ile Lys Ile Ala Asp
775                 780                 785                 790

ttt ggc atg agc cgg aac ctc tat gct ggg gac tat tac cgt gtg cag      2754
Phe Gly Met Ser Arg Asn Leu Tyr Ala Gly Asp Tyr Tyr Arg Val Gln
                795                 800                 805

ggc cgg gca gtg ctg ccc atc cgc tgg atg gcc tgg gag tgc atc ctc      2802
Gly Arg Ala Val Leu Pro Ile Arg Trp Met Ala Trp Glu Cys Ile Leu
            810                 815                 820

atg ggg aag ttc acg act gcg agt gac gtg tgg gcc ttt ggt gtg acc      2850
Met Gly Lys Phe Thr Thr Ala Ser Asp Val Trp Ala Phe Gly Val Thr
        825                 830                 835

ctg tgg gag gtg ctg atg ctc tgt agg gcc cag ccc ttt ggg tca gct      2898
Leu Trp Glu Val Leu Met Leu Cys Arg Ala Gln Pro Phe Gly Ser Ala
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840 845 850

cac cga cga gca ggt cat cga gaa cgc ggg gga gtt ctt ccg gga cca 2946
His Arg Arg Ala Gly His Arg Glu Arg Gly Gly Val Leu Pro Gly Pro
855 860 865 870

ggg ccg gca gtg tac ctg tcc cgg ccg cct gcc tgc ccg cag ggc cta 2994
Gly Pro Ala Val Tyr Leu Ser Arg Pro Pro Ala Cys Pro Gln Gly Leu
875 880 885

tat gag ctg atg ctt cgg tgc tgg agc cgg gag tct gag cag cga cca 3042
Tyr Glu Leu Met Leu Arg Cys Trp Ser Arg Glu Ser Glu Gln Arg Pro
890 895 900

ccc ttt tcc cag ctg cat cgg ttc ctg gca gag gat gca ctc aac acg 3090
Pro Phe Ser Gln Leu His Arg Phe Leu Ala Glu Asp Ala Leu Asn Thr
905 910 915

gtg tgaatcacac atccagctgc ccctccctca gggagcgatc caggggaagc 3143
Val

cagtgacact aaaacaagag gacacaatgg cacctctgcc cttcccctcc cgacagccca 3203

tcacctctaa tagaggcagt gagactgcag gtgggctggg cccacccagg gagctgatgc 3263

cccttctccc cttcctggac acactctcat gtccccttcc tgttcttcct tcctagaagc 3323

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Tyr Ala Leu Gly Met Gln Asp Arg Thr Ile Pro Asp Ser Asp Ile Ser
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Ala Ser Ser Ser Trp Ser Asp Ser Thr Ala Ala Arg His Ser Arg Leu
    50                  55                  60

Glu Ser Ser Asp Gly Asp Gly Ala Trp Cys Pro Ala Gly Ser Val Phe
65                  70                  75                  80

Pro Lys Glu Glu Glu Tyr Leu Gln Val Asp Leu Gln Arg Leu His Leu
                85                  90                  95

Val Ala Leu Val Gly Thr Gln Gly Arg His Ala Gly Gly Leu Gly Lys
            100                 105                 110

Glu Phe Ser Arg Ser Tyr Arg Leu Arg Tyr Ser Arg Asp Gly Arg Arg
        115                 120                 125

Trp Met Gly Trp Lys Asp Arg Trp Gly Gln Glu Val Ile Ser Gly Asn
    130                 135                 140

Glu Asp Pro Glu Gly Val Val Leu Lys Asp Leu Gly Pro Pro Met Val
145                 150                 155                 160

Ala Arg Leu Val Arg Phe Tyr Pro Arg Ala Asp Arg Val Met Ser Val
                165                 170                 175

Cys Leu Arg Val Glu Leu Tyr Gly Cys Leu Trp Arg Asp Gly Leu Leu
            180                 185                 190

Ser Tyr Thr Ala Pro Val Gly Gln Thr Met Tyr Leu Ser Glu Ala Val
        195                 200                 205

Tyr Leu Asn Asp Ser Thr Tyr Asp Gly His Thr Val Gly Gly Leu Gln
    210                 215                 220

Tyr Gly Gly Leu Gly Gln Leu Ala Asp Gly Val Val Gly Leu Asp Asp
225                 230                 235                 240

Phe Arg Lys Ser Gln Glu Leu Arg Val Trp Pro Gly Tyr Asp Tyr Val
                245                 250                 255

Gly Trp Ser Asn His Ser Phe Ser Ser Gly Tyr Val Glu Met Glu Phe
            260                 265                 270

Glu Phe Asp Arg Leu Arg Ala Phe Gln Ala Met Gln Val His Cys Asn
        275                 280                 285

Asn Met His Thr Leu Gly Ala Arg Leu Pro Gly Gly Val Glu Cys Arg
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290 295 300

Phe Arg Arg Gly Pro Ala Met Ala Trp Glu Gly Glu Pro Met Arg His
305 310 315 320

Asn Leu Gly Gly Asn Leu Gly Asp Pro Arg Ala Arg Ala Val Ser Val
325 330 335

Pro Leu Gly Gly Arg Val Ala Arg Phe Leu Gln Cys Arg Phe Leu Phe
340 345 350

Ala Gly Pro Trp Leu Leu Phe Ser Glu Ile Ser Phe Ile Ser Asp Val
355 360 365

Val Asn Asn Ser Ser Pro Ala Leu Gly Gly Thr Phe Pro Pro Ala Pro
370 375 380

Trp Trp Pro Pro Gly Pro Pro Pro Thr Asn Phe Ser Ser Leu Glu Leu
385 390 395 400

Glu Pro Arg Gly Gln Gln Pro Val Ala Lys Ala Glu Gly Ser Pro Thr
405 410 415

Ala Ile Leu Ile Gly Cys Leu Val Ala Ile Ile Leu Leu Leu Leu Leu
420 425 430

Ile Ile Ala Leu Met Leu Trp Arg Leu His Trp Arg Arg Leu Leu Ser
435 440 445

Lys Ala Glu Arg Arg Val Leu Glu Glu Glu Leu Thr Val His Leu Ser
450 455 460

Val Pro Gly Asp Thr Ile Leu Ile Asn Asn Arg Pro Gly Pro Arg Glu
465 470 475 480

Pro Pro Pro Tyr Gln Glu Pro Arg Pro Arg Gly Asn Pro Pro His Ser
485 490 495

Ala Pro Cys Val Pro Asn Gly Ser Ala Leu Leu Leu Ser Asn Pro Ala
500 505 510

Tyr Arg Leu Leu Leu Ala Thr Tyr Ala Arg Pro Pro Arg Gly Pro Gly
515 520 525

Pro Pro Thr Pro Ala Trp Ala Lys Pro Thr Asn Thr Gln Ala Tyr Ser
530 535 540

Gly Asp Tyr Met Glu Pro Glu Lys Pro Gly Ala Pro Leu Leu Pro Pro
545 550 555 560

Pro Pro Gln Asn Ser Val Pro His Tyr Ala Glu Ala Asp Ile Val Thr
565 570 575

Leu Gln Gly Val Thr Gly Gly Asn Thr Tyr Ala Val Pro Ala Leu Pro
580 585 590

Pro Gly Ala Val Gly Asp Gly Pro Pro Arg Val Asp Phe Pro Arg Ser
595 600 605

Arg Leu Arg Phe Lys Glu Lys Leu Gly Glu Gly Gln Phe Gly Glu Val
610 615 620

His Leu Cys Glu Val Asp Ser Pro Gln Asp Leu Val Ser Leu Asp Phe
625 630 635 640

Pro Leu Asn Val Arg Lys Gly His Pro Leu Leu Val Ala Val Lys Ile
645 650 655

Leu Arg Pro Asp Ala Thr Lys Asn Ala Ser Phe Ser Leu Phe Ser Arg
660 665 670

Asn Asp Phe Leu Lys Glu Val Lys Ile Met Ser Arg Leu Lys Asp Pro
675 680 685

Asn Ile Ile Arg Leu Leu Gly Val Cys Val Gln Asp Asp Pro Leu Cys
690 695 700

Met Ile Thr Asp Tyr Met Glu Asn Gly Asp Leu Asn Gln Phe Leu Ser
705 710 715 720

Ala His Gln Leu Glu Asp Lys Ala Ala Glu Gly Ala Pro Gly Asp Gly
725 730 735

Gln Ala Ala Gln Gly Pro Thr Ile Ser Tyr Pro Met Leu Leu His Val
740 745 750

Ala Ala Gln Ile Ala Ser Gly Met Arg Tyr Leu Ala Thr Leu Asn Phe
755 760 765

Val His Arg Asp Leu Ala Thr Arg Asn Cys Leu Val Gly Glu Asn Phe
770 775 780

Thr Ile Lys Ile Ala Asp Phe Gly Met Ser Arg Asn Leu Tyr Ala Gly
785 790 795 800

Asp Tyr Tyr Arg Val Gln Gly Arg Ala Val Leu Pro Ile Arg Trp Met
805 810 815

Ala Trp Glu Cys Ile Leu Met Gly Lys Phe Thr Thr Ala Ser Asp Val
820 825 830

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Trp Ala Phe Gly Val Thr Leu Trp Glu Val Leu Met Leu Cys Arg Ala
        835                 840                 845

Gln Pro Phe Gly Ser Ala His Arg Arg Ala Gly His Arg Glu Arg Gly
    850                 855                 860

Gly Val Leu Pro Gly Pro Gly Pro Ala Val Tyr Leu Ser Arg Pro Pro
865                 870                 875                 880

Ala Cys Pro Gln Gly Leu Tyr Glu Leu Met Leu Arg Cys Trp Ser Arg
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Glu Ser Glu Gln Arg Pro Pro Phe Ser Gln Leu His Arg Phe Leu Ala
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Glu Asp Ala Leu Asn Thr Val
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gtcacc atg gaa gtg tca cca ttg cag cct gta aat gaa aat atg caa         168
       Met Glu Val Ser Pro Leu Gln Pro Val Asn Glu Asn Met Gln
       1               5                   10

gtc aac aaa ata aag aaa aat gaa gat gct aag aaa aga ctg tct gtt        216
Val Asn Lys Ile Lys Lys Asn Glu Asp Ala Lys Lys Arg Leu Ser Val
15                  20                  25                  30

gaa aga atc tat caa aag aaa aca caa ttg gaa cat att ttg ctc cgc        264
Glu Arg Ile Tyr Gln Lys Lys Thr Gln Leu Glu His Ile Leu Leu Arg
                35                  40                  45

cca gac acc tac att ggt tct gtg gaa tta gtg acc cag caa atg tgg        312
Pro Asp Thr Tyr Ile Gly Ser Val Glu Leu Val Thr Gln Gln Met Trp
            50                  55                  60

gtt tac gat gaa gat gtt ggc att aac tat agg gaa gtc act ttt gtt        360
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Val Tyr Asp Glu Asp Val Gly Ile Asn Tyr Arg Glu Val Thr Phe Val
        65                  70                  75

cct ggt ttg tac aaa atc ttt gat gag att cta gtt aat gct gcg gac      408
Pro Gly Leu Tyr Lys Ile Phe Asp Glu Ile Leu Val Asn Ala Ala Asp
    80                  85                  90

aac aaa caa agg gac cca aaa atg tct tgt att aga gtc aca att gat      456
Asn Lys Gln Arg Asp Pro Lys Met Ser Cys Ile Arg Val Thr Ile Asp
95                  100                 105                 110

ccg gaa aac aat tta att agt ata tgg aat aat gga aaa ggt att cct      504
Pro Glu Asn Asn Leu Ile Ser Ile Trp Asn Asn Gly Lys Gly Ile Pro
                115                 120                 125

gtt gtt gaa cac aaa gtt gaa aag atg tat gtc cca gct ctc ata ttt      552
Val Val Glu His Lys Val Glu Lys Met Tyr Val Pro Ala Leu Ile Phe
            130                 135                 140

gga cag ctc cta act tct agt aac tat gat gat gat gaa aag aaa gtg      600
Gly Gln Leu Leu Thr Ser Ser Asn Tyr Asp Asp Asp Glu Lys Lys Val
        145                 150                 155

aca ggt ggt cga aat ggc tat gga gcc aaa ttg tgt aac ata ttc agt      648
Thr Gly Gly Arg Asn Gly Tyr Gly Ala Lys Leu Cys Asn Ile Phe Ser
    160                 165                 170

acc aaa ttt act gtg gaa aca gcc agt aga gaa tac aag aaa atg ttc      696
Thr Lys Phe Thr Val Glu Thr Ala Ser Arg Glu Tyr Lys Lys Met Phe
175                 180                 185                 190

aaa cag aca tgg atg gat aat atg gga aga gct ggt gag atg gaa ctc      744
Lys Gln Thr Trp Met Asp Asn Met Gly Arg Ala Gly Glu Met Glu Leu
                195                 200                 205

aag ccc ttc aat gga gaa gat tat aca tgt atc acc ttt cag cct gat      792
Lys Pro Phe Asn Gly Glu Asp Tyr Thr Cys Ile Thr Phe Gln Pro Asp
            210                 215                 220

ttg tct aag ttt aaa atg caa agc ctg gac aaa gat att gtt gca cta      840
Leu Ser Lys Phe Lys Met Gln Ser Leu Asp Lys Asp Ile Val Ala Leu
        225                 230                 235

atg gtc aga aga gca tat gat att gct gga tcc acc aaa gat gtc aaa      888
Met Val Arg Arg Ala Tyr Asp Ile Ala Gly Ser Thr Lys Asp Val Lys
    240                 245                 250

gtc ttt ctt aat gga aat aaa ctg cca gta aaa gga ttt cgt agt tat      936
Val Phe Leu Asn Gly Asn Lys Leu Pro Val Lys Gly Phe Arg Ser Tyr
255                 260                 265                 270

gtg gac atg tat ttg aag gac aag ttg gat gaa act ggt aac tcc ttg      984
Val Asp Met Tyr Leu Lys Asp Lys Leu Asp Glu Thr Gly Asn Ser Leu
                275                 280                 285

aaa gta ata cat gaa caa gta aac cac agg tgg gaa gtg tgt tta act      1032
Lys Val Ile His Glu Gln Val Asn His Arg Trp Glu Val Cys Leu Thr
            290                 295                 300

atg agt gaa aaa ggc ttt cag caa att agc ttt gtc aac agc att gct      1080
Met Ser Glu Lys Gly Phe Gln Gln Ile Ser Phe Val Asn Ser Ile Ala
        305                 310                 315

aca tcc aag ggt ggc aga cat gtt gat tat gta gct gat cag att gtg      1128
Thr Ser Lys Gly Gly Arg His Val Asp Tyr Val Ala Asp Gln Ile Val
    320                 325                 330
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act aaa ctt gtt gat gtt gtg aag aag aag aac aag ggt ggt gtt gca      1176
Thr Lys Leu Val Asp Val Val Lys Lys Lys Asn Lys Gly Gly Val Ala
335                 340                 345                 350

gta aaa gca cat cag gtg aaa aat cac atg tgg att ttt gta aat gcc      1224
Val Lys Ala His Gln Val Lys Asn His Met Trp Ile Phe Val Asn Ala
                355                 360                 365

tta att gaa aac cca acc ttt gac tct cag aca aaa gaa aac atg act      1272
Leu Ile Glu Asn Pro Thr Phe Asp Ser Gln Thr Lys Glu Asn Met Thr
            370                 375                 380

tta caa ccc aag agc ttt gga tca aca tgc caa ttg agt gaa aaa ttt      1320
Leu Gln Pro Lys Ser Phe Gly Ser Thr Cys Gln Leu Ser Glu Lys Phe
        385                 390                 395

atc aaa gct gcc att ggc tgt ggt att gta gaa agc ata cta aac tgg      1368
Ile Lys Ala Ala Ile Gly Cys Gly Ile Val Glu Ser Ile Leu Asn Trp
    400                 405                 410

gtg aag ttt aag gcc caa gtc cag tta aac aag aag tgt tca gct gta      1416
Val Lys Phe Lys Ala Gln Val Gln Leu Asn Lys Lys Cys Ser Ala Val
415                 420                 425                 430

aaa cat aat aga atc aag gga att ccc aaa ctc gat gat gcc aat gat      1464
Lys His Asn Arg Ile Lys Gly Ile Pro Lys Leu Asp Asp Ala Asn Asp
                435                 440                 445

gca ggg ggc cga aac tcc act gag tgt acg ctt atc ctg act gag gga      1512
Ala Gly Gly Arg Asn Ser Thr Glu Cys Thr Leu Ile Leu Thr Glu Gly
            450                 455                 460

gat tca gcc aaa act ttg gct gtt tca ggc ctt ggt gtg gtt ggg aga      1560
Asp Ser Ala Lys Thr Leu Ala Val Ser Gly Leu Gly Val Val Gly Arg
        465                 470                 475

gac aaa tat ggg gtt ttc cct ctt aga gga aaa ata ctc aat gtt cga      1608
Asp Lys Tyr Gly Val Phe Pro Leu Arg Gly Lys Ile Leu Asn Val Arg
    480                 485                 490

gaa gct tct cat aag cag atc atg gaa aat gct gag att aac aat atc      1656
Glu Ala Ser His Lys Gln Ile Met Glu Asn Ala Glu Ile Asn Asn Ile
495                 500                 505                 510

atc aag att gtg ggt ctt cag tac aag aaa aac tat gaa gat gaa gat      1704
Ile Lys Ile Val Gly Leu Gln Tyr Lys Lys Asn Tyr Glu Asp Glu Asp
                515                 520                 525

tca ttg aag acg ctt cgt tat ggg aag ata atg att atg aca gat cag      1752
Ser Leu Lys Thr Leu Arg Tyr Gly Lys Ile Met Ile Met Thr Asp Gln
            530                 535                 540

gac caa gat ggt tcc cac atc aaa ggc ttg ctg att aat ttt atc cat      1800
Asp Gln Asp Gly Ser His Ile Lys Gly Leu Leu Ile Asn Phe Ile His
        545                 550                 555

cac aac tgg ccc tct ctt ctg cga cat cgt ttt ctg gag gaa ttt atc      1848
His Asn Trp Pro Ser Leu Leu Arg His Arg Phe Leu Glu Glu Phe Ile
    560                 565                 570

act ccc att gta aag gta tct aaa aac aag caa gaa atg gca ttt tac      1896
Thr Pro Ile Val Lys Val Ser Lys Asn Lys Gln Glu Met Ala Phe Tyr
575                 580                 585                 590

agc ctt cct gaa ttt gaa gag tgg aag agt tct act cca aat cat aaa      1944
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Ser Leu Pro Glu Phe Glu Glu Trp Lys Ser Ser Thr Pro Asn His Lys
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aaa tgg aaa gtc aaa tat tac aaa ggt ttg ggc acc agc aca tca aag      1992
Lys Trp Lys Val Lys Tyr Tyr Lys Gly Leu Gly Thr Ser Thr Ser Lys
            610                 615                 620

gaa gct aaa gaa tac ttt gca gat atg aaa aga cat cgt atc cag ttc      2040
Glu Ala Lys Glu Tyr Phe Ala Asp Met Lys Arg His Arg Ile Gln Phe
        625                 630                 635

aaa tat tct ggt cct gaa gat gat gct gct atc agc ctg gcc ttt agc      2088
Lys Tyr Ser Gly Pro Glu Asp Asp Ala Ala Ile Ser Leu Ala Phe Ser
    640                 645                 650

aaa aaa cag ata gat gat cga aag gaa tgg tta act aat ttc atg gag      2136
Lys Lys Gln Ile Asp Asp Arg Lys Glu Trp Leu Thr Asn Phe Met Glu
655                 660                 665                 670

gat aga aga caa cga aag tta ctt ggg ctt cct gag gat tac ttg tat      2184
Asp Arg Arg Gln Arg Lys Leu Leu Gly Leu Pro Glu Asp Tyr Leu Tyr
                675                 680                 685

gga caa act acc aca tat ctg aca tat aat gac ttc atc aac aag gaa      2232
Gly Gln Thr Thr Thr Tyr Leu Thr Tyr Asn Asp Phe Ile Asn Lys Glu
            690                 695                 700

ctt atc ttg ttc tca aat tct gat aac gag aga tct atc cct tct atg      2280
Leu Ile Leu Phe Ser Asn Ser Asp Asn Glu Arg Ser Ile Pro Ser Met
        705                 710                 715

gtg gat ggt ttg aaa cca ggt cag aga aag gtt ttg ttt act tgc ttc      2328
Val Asp Gly Leu Lys Pro Gly Gln Arg Lys Val Leu Phe Thr Cys Phe
    720                 725                 730

aaa cgg aat gac aag cga gaa gta aag gtt gcc caa tta gct gga tca      2376
Lys Arg Asn Asp Lys Arg Glu Val Lys Val Ala Gln Leu Ala Gly Ser
735                 740                 745                 750

gtg gct gaa atg tct tct tat cat cat ggt gag atg tca cta atg atg      2424
Val Ala Glu Met Ser Ser Tyr His His Gly Glu Met Ser Leu Met Met
                755                 760                 765

acc att atc aat ttg gct cag aat ttt gtg ggt agc aat aat cta aac      2472
Thr Ile Ile Asn Leu Ala Gln Asn Phe Val Gly Ser Asn Asn Leu Asn
            770                 775                 780

ctc ttg cag ccc att ggt cag ttt ggt acc agg cta cat ggt ggc aag      2520
Leu Leu Gln Pro Ile Gly Gln Phe Gly Thr Arg Leu His Gly Gly Lys
        785                 790                 795

gat tct gct agt cca cga tac atc ttt aca atg ctc agc tct ttg gct      2568
Asp Ser Ala Ser Pro Arg Tyr Ile Phe Thr Met Leu Ser Ser Leu Ala
    800                 805                 810

cga ttg tta ttt cca cca aaa gat gat cac acg ttg aag ttt tta tat      2616
Arg Leu Leu Phe Pro Pro Lys Asp Asp His Thr Leu Lys Phe Leu Tyr
815                 820                 825                 830

gat gac aac cag cgt gtt gag cct gaa tgg tac att cct att att ccc      2664
Asp Asp Asn Gln Arg Val Glu Pro Glu Trp Tyr Ile Pro Ile Ile Pro
                835                 840                 845

atg gtg ctg ata aat ggt gct gaa gga atc ggt act ggg tgg tcc tgc      2712
Met Val Leu Ile Asn Gly Ala Glu Gly Ile Gly Thr Gly Trp Ser Cys
            850                 855                 860
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Lys Ile Pro Asn Phe Asp Val Arg Glu Ile Val Asn Asn Ile Arg Arg
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ttg atg gat gga gaa gaa cct ttg cca atg ctt cca agt tac aag aac      2808
Leu Met Asp Gly Glu Glu Pro Leu Pro Met Leu Pro Ser Tyr Lys Asn
    880                 885                 890

ttc aag ggt act att gaa gaa ctg gct cca aat caa tat gtg att agt      2856
Phe Lys Gly Thr Ile Glu Glu Leu Ala Pro Asn Gln Tyr Val Ile Ser
895                 900                 905                 910

ggt gaa gta gct att ctt aat tct aca acc att gaa atc tca gag ctt      2904
Gly Glu Val Ala Ile Leu Asn Ser Thr Thr Ile Glu Ile Ser Glu Leu
                915                 920                 925

ccc gtc aga aca tgg acc cag aca tac aaa gaa caa gtt cta gaa ccc      2952
Pro Val Arg Thr Trp Thr Gln Thr Tyr Lys Glu Gln Val Leu Glu Pro
            930                 935                 940

atg ttg aat ggc acc gag aag aca cct cct ctc ata aca gac tat agg      3000
Met Leu Asn Gly Thr Glu Lys Thr Pro Pro Leu Ile Thr Asp Tyr Arg
        945                 950                 955

gaa tac cat aca gat acc act gtg aaa ttt gtt gtg aag atg act gaa      3048
Glu Tyr His Thr Asp Thr Thr Val Lys Phe Val Val Lys Met Thr Glu
    960                 965                 970

gaa aaa ctg gca gag gca gag aga gtt gga cta cac aaa gtc ttc aaa      3096
Glu Lys Leu Ala Glu Ala Glu Arg Val Gly Leu His Lys Val Phe Lys
975                 980                 985                 990

ctc caa act agt ctc aca tgc aac tct atg  gtg ctt ttt gac cac  gta    3144
Leu Gln Thr Ser Leu Thr Cys Asn Ser Met  Val Leu Phe Asp His  Val
                995                 1000                1005

ggc tgt tta aag  aaa tat gac acg gtg  ttg gat att cta aga  gac       3189
Gly Cys Leu Lys  Lys Tyr Asp Thr Val  Leu Asp Ile Leu Arg  Asp
            1010                 1015                 1020

ttt ttt gaa ctc  aga ctt aaa tat tat  gga tta aga aaa gaa  tgg       3234
Phe Phe Glu Leu  Arg Leu Lys Tyr Tyr  Gly Leu Arg Lys Glu  Trp
            1025                 1030                 1035

ctc cta gga atg  ctt ggt gct gaa tct  gct aaa ctg aat aat  cag       3279
Leu Leu Gly Met  Leu Gly Ala Glu Ser  Ala Lys Leu Asn Asn  Gln
            1040                 1045                 1050

gct cgc ttt atc  tta gag aaa ata gat  ggc aaa ata atc att  gaa       3324
Ala Arg Phe Ile  Leu Glu Lys Ile Asp  Gly Lys Ile Ile Ile  Glu
            1055                 1060                 1065

aat aag cct aag  aaa gaa tta att aaa  gtt ctg att cag agg  gga       3369
Asn Lys Pro Lys  Lys Glu Leu Ile Lys  Val Leu Ile Gln Arg  Gly
            1070                 1075                 1080

tat gat tcg gat  cct gtg aag gcc tgg  aaa gaa gcc cag caa  aag       3414
Tyr Asp Ser Asp  Pro Val Lys Ala Trp  Lys Glu Ala Gln Gln  Lys
            1085                 1090                 1095

gtt cca gat gaa  gaa gaa aat gaa gag  agt gac aac gaa aag  gaa       3459
Val Pro Asp Glu  Glu Glu Asn Glu Glu  Ser Asp Asn Glu Lys  Glu
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act gaa aag agt  gac tcc gta aca gat  tct gga cca acc ttc  aac       3504
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Thr Glu Lys Ser  Asp Ser Val Thr Asp  Ser Gly Pro Thr Phe  Asn
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tat ctt ctt gat  atg ccc ctt tgg tat  tta acc aag gaa aag  aaa      3549
Tyr Leu Leu Asp  Met Pro Leu Trp Tyr  Leu Thr Lys Glu Lys  Lys
            1130                 1135                 1140

gat gaa ctc tgc  agg cta aga aat gaa  aaa gaa caa gag ctg  gac      3594
Asp Glu Leu Cys  Arg Leu Arg Asn Glu  Lys Glu Gln Glu Leu  Asp
            1145                 1150                 1155

aca tta aaa aga  aag agt cca tca gat  ttg tgg aaa gaa gac  ttg      3639
Thr Leu Lys Arg  Lys Ser Pro Ser Asp  Leu Trp Lys Glu Asp  Leu
            1160                 1165                 1170

gct aca ttt att  gaa gaa ttg gag gct  gtt gaa gcc aag gaa  aaa      3684
Ala Thr Phe Ile  Glu Glu Leu Glu Ala  Val Glu Ala Lys Glu  Lys
            1175                 1180                 1185

caa gat gaa caa  gtc gga ctt cct ggg  aaa ggg ggg aag gcc  aag      3729
Gln Asp Glu Gln  Val Gly Leu Pro Gly  Lys Gly Gly Lys Ala  Lys
            1190                 1195                 1200

ggg aaa aaa aca  caa atg gct gaa gtt  ttg cct tct ccg cgt  ggt      3774
Gly Lys Lys Thr  Gln Met Ala Glu Val  Leu Pro Ser Pro Arg  Gly
            1205                 1210                 1215

caa aga gtc att  cca cga ata acc ata  gaa atg aaa gca gag  gca      3819
Gln Arg Val Ile  Pro Arg Ile Thr Ile  Glu Met Lys Ala Glu  Ala
            1220                 1225                 1230

gaa aag aaa aat  aaa aag aaa att aag  aat gaa aat act gaa  gga      3864
Glu Lys Lys Asn  Lys Lys Lys Ile Lys  Asn Glu Asn Thr Glu  Gly
            1235                 1240                 1245

agc cct caa gaa  gat ggt gtg gaa cta  gaa ggc cta aaa caa  aga      3909
Ser Pro Gln Glu  Asp Gly Val Glu Leu  Glu Gly Leu Lys Gln  Arg
            1250                 1255                 1260

tta gaa aag aaa  cag aaa aga gaa cca  ggt aca aag aca aag  aaa      3954
Leu Glu Lys Lys  Gln Lys Arg Glu Pro  Gly Thr Lys Thr Lys  Lys
            1265                 1270                 1275

caa act aca ttg  gca ttt aag cca atc  aaa aaa gga aag aag  aga      3999
Gln Thr Thr Leu  Ala Phe Lys Pro Ile  Lys Lys Gly Lys Lys  Arg
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aat ccc tgg tct  gat tca gaa tca gat  agg agc agt gac gaa  agt      4044
Asn Pro Trp Ser  Asp Ser Glu Ser Asp  Arg Ser Ser Asp Glu  Ser
            1295                 1300                 1305

aat ttt gat gtc  cct cca cga gaa aca  gag cca cgg aga gca  gca      4089
Asn Phe Asp Val  Pro Pro Arg Glu Thr  Glu Pro Arg Arg Ala  Ala
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aca aaa aca aaa  ttc aca atg gat ttg  gat tca gat gaa gat  ttc      4134
Thr Lys Thr Lys  Phe Thr Met Asp Leu  Asp Ser Asp Glu Asp  Phe
            1325                 1330                 1335

tca gat ttt gat  gaa aaa act gat gat  gaa gat ttt gtc cca  tca      4179
Ser Asp Phe Asp  Glu Lys Thr Asp Asp  Glu Asp Phe Val Pro  Ser
            1340                 1345                 1350

gat gct agt cca  cct aag acc aaa act  tcc cca aaa ctt agt  aac      4224
Asp Ala Ser Pro  Pro Lys Thr Lys Thr  Ser Pro Lys Leu Ser  Asn
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aaa gaa ctg aaa  cca cag aaa agt gtc  gtg tca gac ctt gaa  gct      4269
Lys Glu Leu Lys  Pro Gln Lys Ser Val  Val Ser Asp Leu Glu  Ala
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gat gat gtt aag  ggc agt gta cca ctg  tct tca agc cct cct  gct      4314
Asp Asp Val Lys  Gly Ser Val Pro Leu  Ser Ser Ser Pro Pro  Ala
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aca cat ttc cca  gat gaa act gaa att  aca aac cca gtt cct  aaa      4359
Thr His Phe Pro  Asp Glu Thr Glu Ile  Thr Asn Pro Val Pro  Lys
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aag aat gtg aca  gtg aag aag aca gca  gca aaa agt cag tct  tcc      4404
Lys Asn Val Thr  Val Lys Lys Thr Ala  Ala Lys Ser Gln Ser  Ser
            1415                 1420                 1425

acc tcc act acc  ggt gcc aaa aaa agg  gct gcc cca aaa gga  act      4449
Thr Ser Thr Thr  Gly Ala Lys Lys Arg  Ala Ala Pro Lys Gly  Thr
            1430                 1435                 1440

aaa agg gat cca  gct ttg aat tct ggt  gtc tct caa aag cct  gat      4494
Lys Arg Asp Pro  Ala Leu Asn Ser Gly  Val Ser Gln Lys Pro  Asp
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cct gcc aaa acc  aag aat cgc cgc aaa  agg aag cca tcc act  tct      4539
Pro Ala Lys Thr  Lys Asn Arg Arg Lys  Arg Lys Pro Ser Thr  Ser
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gat gat tct gac  tct aat ttt gag aaa  att gtt tcg aaa gca  gtc      4584
Asp Asp Ser Asp  Ser Asn Phe Glu Lys  Ile Val Ser Lys Ala  Val
            1475                 1480                 1485

aca agc aag aaa  tcc aag ggg gag agt  gat gac ttc cat atg  gac      4629
Thr Ser Lys Lys  Ser Lys Gly Glu Ser  Asp Asp Phe His Met  Asp
            1490                 1495                 1500

ttt gac tca gct  gtg gct cct cgg gca  aaa tct gta cgg gca  aag      4674
Phe Asp Ser Ala  Val Ala Pro Arg Ala  Lys Ser Val Arg Ala  Lys
            1505                 1510                 1515

aaa cct ata aag  tac ctg gaa gag tca  gat gaa gat gat ctg  ttt      4719
Lys Pro Ile Lys  Tyr Leu Glu Glu Ser  Asp Glu Asp Asp Leu  Phe
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caagacatca aagtgaagta aagcccaagt gttctttagc tttttataat actgtctaaa   4899

tagtgaccat ctcatgggca ttgttttctt ctctgctttg tctgtgtttt gagtctgctt   4959

tcttttgtct ttaaaacctg atttttaagt tcttctgaac tgtagaaata gctatctgat   5019

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aattgctcat gttcttcatc ttctcaaatc atcagaggcc aaagaaaaac actttggctg   5319

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Ile Tyr Gln Lys Lys Thr Gln Leu Glu His Ile Leu Leu Arg Pro Asp
35 40 45

Thr Tyr Ile Gly Ser Val Glu Leu Val Thr Gln Gln Met Trp Val Tyr
50 55 60

Asp Glu Asp Val Gly Ile Asn Tyr Arg Glu Val Thr Phe Val Pro Gly
65 70 75 80

Leu Tyr Lys Ile Phe Asp Glu Ile Leu Val Asn Ala Ala Asp Asn Lys
85 90 95

Gln Arg Asp Pro Lys Met Ser Cys Ile Arg Val Thr Ile Asp Pro Glu
100 105 110

Asn Asn Leu Ile Ser Ile Trp Asn Asn Gly Lys Gly Ile Pro Val Val
115 120 125

Glu His Lys Val Glu Lys Met Tyr Val Pro Ala Leu Ile Phe Gly Gln

130 135 140

Leu Leu Thr Ser Ser Asn Tyr Asp Asp Asp Glu Lys Lys Val Thr Gly
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Gly Arg Asn Gly Tyr Gly Ala Lys Leu Cys Asn Ile Phe Ser Thr Lys
165 170 175

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Phe Thr Val Glu Thr Ala Ser Arg Glu Tyr Lys Lys Met Phe Lys Gln
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Thr Trp Met Asp Asn Met Gly Arg Ala Gly Glu Met Glu Leu Lys Pro
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Phe Asn Gly Glu Asp Tyr Thr Cys Ile Thr Phe Gln Pro Asp Leu Ser
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Lys Phe Lys Met Gln Ser Leu Asp Lys Asp Ile Val Ala Leu Met Val
225                 230                 235                 240

Arg Arg Ala Tyr Asp Ile Ala Gly Ser Thr Lys Asp Val Lys Val Phe
                245                 250                 255

Leu Asn Gly Asn Lys Leu Pro Val Lys Gly Phe Arg Ser Tyr Val Asp
            260                 265                 270

Met Tyr Leu Lys Asp Lys Leu Asp Glu Thr Gly Asn Ser Leu Lys Val
        275                 280                 285

Ile His Glu Gln Val Asn His Arg Trp Glu Val Cys Leu Thr Met Ser
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Glu Lys Gly Phe Gln Gln Ile Ser Phe Val Asn Ser Ile Ala Thr Ser
305                 310                 315                 320

Lys Gly Gly Arg His Val Asp Tyr Val Ala Asp Gln Ile Val Thr Lys
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Leu Val Asp Val Val Lys Lys Lys Asn Lys Gly Gly Val Ala Val Lys
            340                 345                 350

Ala His Gln Val Lys Asn His Met Trp Ile Phe Val Asn Ala Leu Ile
        355                 360                 365

Glu Asn Pro Thr Phe Asp Ser Gln Thr Lys Glu Asn Met Thr Leu Gln
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Pro Lys Ser Phe Gly Ser Thr Cys Gln Leu Ser Glu Lys Phe Ile Lys
385                 390                 395                 400

Ala Ala Ile Gly Cys Gly Ile Val Glu Ser Ile Leu Asn Trp Val Lys
                405                 410                 415

Phe Lys Ala Gln Val Gln Leu Asn Lys Lys Cys Ser Ala Val Lys His
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Asn Arg Ile Lys Gly Ile Pro Lys Leu Asp Asp Ala Asn Asp Ala Gly
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Gly Arg Asn Ser Thr Glu Cys Thr Leu Ile Leu Thr Glu Gly Asp Ser
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Ala Lys Thr Leu Ala Val Ser Gly Leu Gly Val Val Gly Arg Asp Lys
465                 470                 475                 480

Tyr Gly Val Phe Pro Leu Arg Gly Lys Ile Leu Asn Val Arg Glu Ala
                485                 490                 495

Ser His Lys Gln Ile Met Glu Asn Ala Glu Ile Asn Asn Ile Ile Lys
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Ile Val Gly Leu Gln Tyr Lys Lys Asn Tyr Glu Asp Glu Asp Ser Leu
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Lys Thr Leu Arg Tyr Gly Lys Ile Met Ile Met Thr Asp Gln Asp Gln
    530                 535                 540

Asp Gly Ser His Ile Lys Gly Leu Leu Ile Asn Phe Ile His His Asn
545                 550                 555                 560

Trp Pro Ser Leu Leu Arg His Arg Phe Leu Glu Glu Phe Ile Thr Pro
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Ile Val Lys Val Ser Lys Asn Lys Gln Glu Met Ala Phe Tyr Ser Leu
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Pro Glu Phe Glu Glu Trp Lys Ser Ser Thr Pro Asn His Lys Lys Trp
        595                 600                 605

Lys Val Lys Tyr Tyr Lys Gly Leu Gly Thr Ser Thr Ser Lys Glu Ala
    610                 615                 620

Lys Glu Tyr Phe Ala Asp Met Lys Arg His Arg Ile Gln Phe Lys Tyr
625                 630                 635                 640

Ser Gly Pro Glu Asp Asp Ala Ala Ile Ser Leu Ala Phe Ser Lys Lys

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Gln Ile Asp Asp Arg Lys Glu Trp Leu Thr Asn Phe Met Glu Asp Arg
            660                 665                 670

Arg Gln Arg Lys Leu Leu Gly Leu Pro Glu Asp Tyr Leu Tyr Gly Gln
        675                 680                 685

Thr Thr Thr Tyr Leu Thr Tyr Asn Asp Phe Ile Asn Lys Glu Leu Ile
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Leu Phe Ser Asn Ser Asp Asn Glu Arg Ser Ile Pro Ser Met Val Asp
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Asn Asp Lys Arg Glu Val Lys Val Ala Gln Leu Ala Gly Ser Val Ala
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Glu Met Ser Ser Tyr His His Gly Glu Met Ser Leu Met Met Thr Ile
755 760 765

Ile Asn Leu Ala Gln Asn Phe Val Gly Ser Asn Asn Leu Asn Leu Leu
770 775 780

Gln Pro Ile Gly Gln Phe Gly Thr Arg Leu His Gly Gly Lys Asp Ser
785 790 795 800

Ala Ser Pro Arg Tyr Ile Phe Thr Met Leu Ser Ser Leu Ala Arg Leu
805 810 815

Leu Phe Pro Pro Lys Asp Asp His Thr Leu Lys Phe Leu Tyr Asp Asp
820 825 830

Asn Gln Arg Val Glu Pro Glu Trp Tyr Ile Pro Ile Ile Pro Met Val
835 840 845

Leu Ile Asn Gly Ala Glu Gly Ile Gly Thr Gly Trp Ser Cys Lys Ile
850 855 860

Pro Asn Phe Asp Val Arg Glu Ile Val Asn Asn Ile Arg Arg Leu Met
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Gly Thr Ile Glu Glu Leu Ala Pro Asn Gln Tyr Val Ile Ser Gly Glu
900 905 910

Val Ala Ile Leu Asn Ser Thr Thr Ile Glu Ile Ser Glu Leu Pro Val
915 920 925

Arg Thr Trp Thr Gln Thr Tyr Lys Glu Gln Val Leu Glu Pro Met Leu
930 935 940

Asn Gly Thr Glu Lys Thr Pro Pro Leu Ile Thr Asp Tyr Arg Glu Tyr
945 950 955 960

His Thr Asp Thr Thr Val Lys Phe Val Val Lys Met Thr Glu Glu Lys
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Leu Ala Glu Ala Glu Arg Val Gly Leu His Lys Val Phe Lys Leu Gln

980 985 990

Thr Ser Leu Thr Cys Asn Ser Met Val Leu Phe Asp His Val Gly Cys
995 1000 1005

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Glu Leu Arg Leu Lys Tyr Tyr Gly Leu Arg Lys Glu Trp Leu Leu
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Gly Met Leu Gly Ala Glu Ser Ala Lys Leu Asn Asn Gln Ala Arg
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Phe Ile Leu Glu Lys Ile Asp Gly Lys Ile Ile Ile Glu Asn Lys
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Pro Lys Lys Glu Leu Ile Lys Val Leu Ile Gln Arg Gly Tyr Asp
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Ser Asp Pro Val Lys Ala Trp Lys Glu Ala Gln Gln Lys Val Pro
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Asp Glu Glu Glu Asn Glu Glu Ser Asp Asn Glu Lys Glu Thr Glu
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Leu Asp Met Pro Leu Trp Tyr Leu Thr Lys Glu Lys Lys Asp Glu
1130 1135 1140

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1250 1255 1260

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Leu Gly Pro Gly Ala Gly Ala Ala Gln Pro Ser Ala Ser Pro Leu Glu
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Val Ala Gln Met Val Thr Leu Leu Ile Ala Phe Ile Cys Val Arg Ser
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Ser Leu Trp Thr Asn Tyr Ser Ala Tyr Ser Tyr Phe Glu Val Val Thr
                70                  75                  80

att tgc gac ttg ata atg atc ctc gcc ttt tac ctg gtc cac ctc ttc       527
Ile Cys Asp Leu Ile Met Ile Leu Ala Phe Tyr Leu Val His Leu Phe
            85                  90                  95

cgc ttc tac cgc gtg ctc acc tgt atc agc tgg ccc ctg tcg gaa ctt       575
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Arg Phe Tyr Arg Val Leu Thr Cys Ile Ser Trp Pro Leu Ser Glu Leu
        100                 105                 110

ctg cac tat tta atc ggt acc ctg ctc ctc ctc atc gcc tcc att gtg       623
Leu His Tyr Leu Ile Gly Thr Leu Leu Leu Leu Ile Ala Ser Ile Val
    115                 120                 125

gca gct tcc aag agt tac aac cag agc gga ctg gta gcc gga gcg atc       671
Ala Ala Ser Lys Ser Tyr Asn Gln Ser Gly Leu Val Ala Gly Ala Ile
130                 135                 140                 145

ttt ggt ttc atg gcc acc ttc ctc tgc atg gca agc ata tgg ctg tcc       719
Phe Gly Phe Met Ala Thr Phe Leu Cys Met Ala Ser Ile Trp Leu Ser
                150                 155                 160

tat aag atc tcg tgt gta acc cag tcc aca gat gca gcc gtc               761
Tyr Lys Ile Ser Cys Val Thr Gln Ser Thr Asp Ala Ala Val
            165                 170                 175

tgatgaggcc acaaccccta ggcccctcag gagctttgca gagaggagga cgtgtactcc     821

aggcgaggcc tctggacctg tgttcctgtg ccaaagtcct gtcaggctgg tgggcaccag     881

gaaaggcctg caccctcttc ctgctctccc aggaagccag ctccctgagc tcctgagcca     941

gccggaaact cttcctccag ccttccgggg agaacatccc tcccattctg ggaaaggaaa    1001

gcagcctcca gggaaatgtt ttctgccttc ctgcttctag aaccacctca ggtactgatg    1061

aaccccactt agcacagctg aaggggtttg tgaatactcc cgcctaaatc ccttctactt    1121

cactcctcag gggagtgaag tgccttaaga aacaaagccc tgtcctaatt tatctagctt    1181

gtcagtccgg tcttagagat accctctttc ctgaagtgag gcgtgcctgt agaaacacta    1241

tgtggtcagc ctgtccccaa ggagatcttg tgtctcctct ccatctctgc ctttgttacc    1301

agtgtgcatg tgtttgtgtg tttttttaata aaatattgac tcggccagtt aaaaaaaaaa    1361

aaaaaaaa                                                             1369
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<400> 32

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Ala Leu Gly Pro Gly Ala Gly Ala Ala Gln Pro Ser Ala Ser Pro Leu
            20                  25                  30

Glu Gly Leu Leu Asp Leu Ser Tyr Pro Arg Thr His Ala Ala Leu Leu
        35                  40                  45

Lys Val Ala Gln Met Val Thr Leu Leu Ile Ala Phe Ile Cys Val Arg
    50                  55                  60
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Ser Ser Leu Trp Thr Asn Tyr Ser Ala Tyr Ser Tyr Phe Glu Val Val
65 70 75 80

Thr Ile Cys Asp Leu Ile Met Ile Leu Ala Phe Tyr Leu Val His Leu
85 90 95

Phe Arg Phe Tyr Arg Val Leu Thr Cys Ile Ser Trp Pro Leu Ser Glu
100 105 110

Leu Leu His Tyr Leu Ile Gly Thr Leu Leu Leu Leu Ile Ala Ser Ile
115 120 125

Val Ala Ala Ser Lys Ser Tyr Asn Gln Ser Gly Leu Val Ala Gly Ala
130 135 140

Ile Phe Gly Phe Met Ala Thr Phe Leu Cys Met Ala Ser Ile Trp Leu
145 150 155 160

Ser Tyr Lys Ile Ser Cys Val Thr Gln Ser Thr Asp Ala Ala Val
165 170 175

<210> 33

<211> 3470

<212> DNA

<213> NM_012112 C20orf1, chromosome 20 open reading frame 1

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<221> CDS

<222> (458)..(2698)

<223>

<400> 33
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ggagtttgga acggctgaag ttcaccttcc agcccctagc gccgttcgcg ccgctaggcc 120

tggcttctga ggcggttgcg gtgctcggtc gccgcctagg cggggcaggg tgcgagcagg 180

ggcttcgggc cacgcttctc ttggcgacag gattttgctg tgaagtccgt ccgggaaacg 240

gaggaaaaaa agagttgcgg gaggctgtcg gctaataacg gttcttgata catatttgcc 300

agacttcaag atttcagaaa aggggtgaaa gagaagattg caactttgag tcagacctgt 360

aggcctgata gactgattaa accacagaag gtgacctgct gagaaaagtg gtacaaatac 420

tgggaaaaac ctgctcttct gcgttaagtg ggagaca atg tca caa gtt aaa agc 475
Met Ser Gln Val Lys Ser
1 5

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tct tat tcc tat gat gcc ccc tcg gat ttc atc aat ttt tca tcc ttg       523
Ser Tyr Ser Tyr Asp Ala Pro Ser Asp Phe Ile Asn Phe Ser Ser Leu
            10                  15                  20

gat gat gaa gga gat act caa aac ata gat tca tgg ttt gag gag aag       571
Asp Asp Glu Gly Asp Thr Gln Asn Ile Asp Ser Trp Phe Glu Glu Lys
        25                  30                  35

gcc aat ttg gag aat aag tta ctg ggg aag aat gga act gga ggg ctt       619
Ala Asn Leu Glu Asn Lys Leu Leu Gly Lys Asn Gly Thr Gly Gly Leu
    40                  45                  50

ttt cag ggc aaa act cct ttg aga aag gct aat ctt cag caa gct att       667
Phe Gln Gly Lys Thr Pro Leu Arg Lys Ala Asn Leu Gln Gln Ala Ile
55                  60                  65                  70

gtc aca cct ttg aaa cca gtt gac aac act tac tac aaa gag gca gaa       715
Val Thr Pro Leu Lys Pro Val Asp Asn Thr Tyr Tyr Lys Glu Ala Glu
                75                  80                  85

aaa gaa aat ctt gtg gaa caa tcc att ccg tca aat gct tgt tct tcc       763
Lys Glu Asn Leu Val Glu Gln Ser Ile Pro Ser Asn Ala Cys Ser Ser
            90                  95                  100

ctg gaa gtt gag gca gcc ata tca aga aaa act cca gcc cag cct cag       811
Leu Glu Val Glu Ala Ala Ile Ser Arg Lys Thr Pro Ala Gln Pro Gln
        105                 110                 115

aga aga tct ctt agg ctt tct gct cag aag gat ttg gaa cag aaa gaa       859
Arg Arg Ser Leu Arg Leu Ser Ala Gln Lys Asp Leu Glu Gln Lys Glu
    120                 125                 130

aag cat cat gta aaa atg aaa gcc aag aga tgt gcc act cct gta atc       907
Lys His His Val Lys Met Lys Ala Lys Arg Cys Ala Thr Pro Val Ile
135                 140                 145                 150

atc gat gaa att cta ccc tct aag aaa atg aaa gtt tct aac aac aaa       955
Ile Asp Glu Ile Leu Pro Ser Lys Lys Met Lys Val Ser Asn Asn Lys
                155                 160                 165

aag aag cca gag gaa gaa ggc agt gct cat caa gat act gct gaa aag      1003
Lys Lys Pro Glu Glu Glu Gly Ser Ala His Gln Asp Thr Ala Glu Lys
            170                 175                 180

aat gca tct tcc cca gag aaa gcc aag ggt aga cat act gtg cct tgt      1051
Asn Ala Ser Ser Pro Glu Lys Ala Lys Gly Arg His Thr Val Pro Cys
        185                 190                 195

atg cca cct gca aag cag aag ttt cta aaa agt act gag gag caa gag      1099
Met Pro Pro Ala Lys Gln Lys Phe Leu Lys Ser Thr Glu Glu Gln Glu
    200                 205                 210

ctg gag aag agt atg aaa atg cag caa gag gtg gtg gag atg cgg aaa      1147
Leu Glu Lys Ser Met Lys Met Gln Gln Glu Val Val Glu Met Arg Lys
215                 220                 225                 230

aag aat gaa gaa ttc aag aaa ctt gct ctg gct gga ata ggg caa cct      1195
Lys Asn Glu Glu Phe Lys Lys Leu Ala Leu Ala Gly Ile Gly Gln Pro
                235                 240                 245

gtg aag aaa tca gtg agc cag gtc acc aaa tca gtt gac ttc cac ttc      1243
Val Lys Lys Ser Val Ser Gln Val Thr Lys Ser Val Asp Phe His Phe
            250                 255                 260

cgc aca gat gag cga atc aaa caa cat cct aag aac cag gag gaa tat      1291
Arg Thr Asp Glu Arg Ile Lys Gln His Pro Lys Asn Gln Glu Glu Tyr
        265                 270                 275
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aag gaa gtg aac ttt aca tct gaa cta cga aag cat cct tca tct cct      1339
Lys Glu Val Asn Phe Thr Ser Glu Leu Arg Lys His Pro Ser Ser Pro
    280                 285                 290

gcc cga gtg act aag gga tgt acc att gtt aag cct ttc aac ctg tcc      1387
Ala Arg Val Thr Lys Gly Cys Thr Ile Val Lys Pro Phe Asn Leu Ser
295                 300                 305                 310

caa gga aag aaa aga aca ttt gat gaa aca gtt tct aca tat gtg ccc      1435
Gln Gly Lys Lys Arg Thr Phe Asp Glu Thr Val Ser Thr Tyr Val Pro
                315                 320                 325

ctt gca cag caa gtt gaa gac ttc cat aaa cga acc cct aac aga tat      1483
Leu Ala Gln Gln Val Glu Asp Phe His Lys Arg Thr Pro Asn Arg Tyr
            330                 335                 340

cat ttg agg agc aag aag gat gat att aac ctg tta ccc tcc aaa tct      1531
His Leu Arg Ser Lys Lys Asp Asp Ile Asn Leu Leu Pro Ser Lys Ser
        345                 350                 355

tct gtg acc aag att tgc aga gac cca cag act cct gta ctg caa acc      1579
Ser Val Thr Lys Ile Cys Arg Asp Pro Gln Thr Pro Val Leu Gln Thr
    360                 365                 370

aaa cac cgt gca cgg gct gtg acc tgc aaa agt aca gca gag ctg gag      1627
Lys His Arg Ala Arg Ala Val Thr Cys Lys Ser Thr Ala Glu Leu Glu
375                 380                 385                 390

gct gag gag ctc gag aaa ttg caa caa tac aaa ttc aaa gca cgt gaa      1675
Ala Glu Glu Leu Glu Lys Leu Gln Gln Tyr Lys Phe Lys Ala Arg Glu
                395                 400                 405

ctt gat ccc aga ata ctt gaa ggt ggg ccc atc ttg ccc aag aaa cca      1723
Leu Asp Pro Arg Ile Leu Glu Gly Gly Pro Ile Leu Pro Lys Lys Pro
            410                 415                 420

cct gtg aaa cca ccc acc gag cct att ggc ttt gat ttg gaa att gag      1771
Pro Val Lys Pro Pro Thr Glu Pro Ile Gly Phe Asp Leu Glu Ile Glu
        425                 430                 435

aaa aga atc cag gag cga gaa tca aag aag aaa aca gag gat gaa cac      1819
Lys Arg Ile Gln Glu Arg Glu Ser Lys Lys Lys Thr Glu Asp Glu His
    440                 445                 450

ttt gaa ttt cat tcc aga cct tgc cct act aag att ttg gaa gat gtt      1867
Phe Glu Phe His Ser Arg Pro Cys Pro Thr Lys Ile Leu Glu Asp Val
455                 460                 465                 470

gtg ggt gtt cct gaa aag aag gta ctt cca atc acc gtc ccc aag tca      1915
Val Gly Val Pro Glu Lys Lys Val Leu Pro Ile Thr Val Pro Lys Ser
                475                 480                 485

cca gcc ttt gca ttg aag aac aga att cga atg ccc acc aaa gaa gat      1963
Pro Ala Phe Ala Leu Lys Asn Arg Ile Arg Met Pro Thr Lys Glu Asp
            490                 495                 500

gag gaa gag gac gaa ccg gta gtg ata aaa gct caa cct gtg cca cat      2011
Glu Glu Glu Asp Glu Pro Val Val Ile Lys Ala Gln Pro Val Pro His
        505                 510                 515

tat ggg gtg cct ttt aag ccc caa atc cca gag gca aga act gtg gaa      2059
Tyr Gly Val Pro Phe Lys Pro Gln Ile Pro Glu Ala Arg Thr Val Glu
    520                 525                 530

ata tgc cct ttc tcg ttt gat tct cga gac aaa gaa cgt cag tta cag      2107
Ile Cys Pro Phe Ser Phe Asp Ser Arg Asp Lys Glu Arg Gln Leu Gln
535                 540                 545                 550
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aag gag aag aaa ata aaa gaa ctg cag aaa ggg gag gtg ccc aag ttc      2155
Lys Glu Lys Lys Ile Lys Glu Leu Gln Lys Gly Glu Val Pro Lys Phe
                555                 560                 565

aag gca ctt ccc ttg cct cat ttt gac acc att aac ctg cca gag aag      2203
Lys Ala Leu Pro Leu Pro His Phe Asp Thr Ile Asn Leu Pro Glu Lys
            570                 575                 580

aag gta aag aat gtg acc cag att gaa cct ttc tgc ttg gag act gac      2251
Lys Val Lys Asn Val Thr Gln Ile Glu Pro Phe Cys Leu Glu Thr Asp
        585                 590                 595

aga aga ggt gct ctg aag gca cag act tgg aag cac cag ctg gaa gaa      2299
Arg Arg Gly Ala Leu Lys Ala Gln Thr Trp Lys His Gln Leu Glu Glu
    600                 605                 610

gaa ctg aga cag cag aaa gaa gca gct tgt ttc aag gct cgt cca aac      2347
Glu Leu Arg Gln Gln Lys Glu Ala Ala Cys Phe Lys Ala Arg Pro Asn
615                 620                 625                 630

acc gtc atc tct cag gag ccc ttt gtt ccc aag aaa gag aag aaa tca      2395
Thr Val Ile Ser Gln Glu Pro Phe Val Pro Lys Lys Glu Lys Lys Ser
                635                 640                 645

gtt gct gag ggc ctt tct ggt tct cta gtt cag gaa cct ttt cag ctg      2443
Val Ala Glu Gly Leu Ser Gly Ser Leu Val Gln Glu Pro Phe Gln Leu
            650                 655                 660

gct act gag aag aga gcc aaa gag cgg cag gag ctg gag aag aga atg      2491
Ala Thr Glu Lys Arg Ala Lys Glu Arg Gln Glu Leu Glu Lys Arg Met
        665                 670                 675

gct gag gta gaa gcc cag aaa gcc cag cag ttg gag gag gcc aga cta      2539
Ala Glu Val Glu Ala Gln Lys Ala Gln Gln Leu Glu Glu Ala Arg Leu
    680                 685                 690

cag gag gaa gag cag aaa aaa gag gag ctg gcc agg cta cgg aga gaa      2587
Gln Glu Glu Glu Gln Lys Lys Glu Glu Leu Ala Arg Leu Arg Arg Glu
695                 700                 705                 710

ctg gtg cat aag gca aat cca ata cgc aag tac cag ggt ctg gag ata      2635
Leu Val His Lys Ala Asn Pro Ile Arg Lys Tyr Gln Gly Leu Glu Ile
                715                 720                 725

aag tca agt gac cag cct ctg act gtg cct gta tct ccc aaa ttc tcc      2683
Lys Ser Ser Asp Gln Pro Leu Thr Val Pro Val Ser Pro Lys Phe Ser
            730                 735                 740

act cga ttc cac tgc taaactcagc tgtgagctgc ggataccgcc cggcaatggg      2738
Thr Arg Phe His Cys
        745

acctgctctt aacctcaaac ctaggaccgt cttgctttgt cattgggcat ggagagaacc    2798

catttctcca gacttttacc tacccgtgcc tgagaaagca tacttgacaa ctgtggactc    2858

cagttttgtt gagaattgtt ttcttacatt actaaggcta ataatgagat gtaactcatg    2918

aatgtctcga ttagactcca tgtagttact tcctttaaac catcagccgg ccttttatat    2978

gggtcttcac tctgactaga atttagtctc tgtgtcagca cagtgtaatc tctattgcta    3038

ttgcccctta cgactctcac cctctcccca cttttttaa aaattttaac cagaaaataa      3098

agatagttaa atcctaagat agagattaag tcatggttta aatgaggaac aatcagtaaa    3158

tcagattctg tcctcttctc tgcataccgt gaatttatag ttaaggatcc ctttgctgtg    3218
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agggtagaaa acctcaccaa ctgcaccagt gaggaagaag actgcgtgga ttcatgggga 3278

gcctcacagc agccacgcag caggctctgg gtggggctgc cgttaaggca cgttctttcc 3338

ttactggtgc tgataacaac agggaaccgt gcagtgtgca ttttaagacc tggcctggaa 3398

taaatacgtt ttgtctttcc ctcaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 3458

aaaaaaaaaa aa 3470

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<212> PRT

<213> NM_012112 C20orf1, chromosome 20 open reading frame 1

<400> 34

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Ile Asn Phe Ser Ser Leu Asp Asp Glu Gly Asp Thr Gln Asn Ile Asp
20 25 30

Ser Trp Phe Glu Glu Lys Ala Asn Leu Glu Asn Lys Leu Leu Gly Lys
35 40 45

Asn Gly Thr Gly Gly Leu Phe Gln Gly Lys Thr Pro Leu Arg Lys Ala
50 55 60

Asn Leu Gln Gln Ala Ile Val Thr Pro Leu Lys Pro Val Asp Asn Thr
65 70 75 80

Tyr Tyr Lys Glu Ala Glu Lys Glu Asn Leu Val Glu Gln Ser Ile Pro
85 90 95

Ser Asn Ala Cys Ser Ser Leu Glu Val Glu Ala Ala Ile Ser Arg Lys
100 105 110

Thr Pro Ala Gln Pro Gln Arg Arg Ser Leu Arg Leu Ser Ala Gln Lys
115 120 125

Asp Leu Glu Gln Lys Glu Lys His His Val Lys Met Lys Ala Lys Arg
130 135 140

Cys Ala Thr Pro Val Ile Ile Asp Glu Ile Leu Pro Ser Lys Lys Met
145 150 155 160

Lys Val Ser Asn Asn Lys Lys Lys Pro Glu Glu Glu Gly Ser Ala His
165 170 175

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Gln Asp Thr Ala Glu Lys Asn Ala Ser Ser Pro Glu Lys Ala Lys Gly
            180                 185                 190

Arg His Thr Val Pro Cys Met Pro Pro Ala Lys Gln Lys Phe Leu Lys
        195                 200                 205

Ser Thr Glu Glu Gln Glu Leu Glu Lys Ser Met Lys Met Gln Gln Glu
    210                 215                 220

Val Val Glu Met Arg Lys Lys Asn Glu Glu Phe Lys Lys Leu Ala Leu
225                 230                 235                 240

Ala Gly Ile Gly Gln Pro Val Lys Lys Ser Val Ser Gln Val Thr Lys
                245                 250                 255

Ser Val Asp Phe His Phe Arg Thr Asp Glu Arg Ile Lys Gln His Pro
            260                 265                 270

Lys Asn Gln Glu Glu Tyr Lys Glu Val Asn Phe Thr Ser Glu Leu Arg
        275                 280                 285

Lys His Pro Ser Ser Pro Ala Arg Val Thr Lys Gly Cys Thr Ile Val
    290                 295                 300

Lys Pro Phe Asn Leu Ser Gln Gly Lys Lys Arg Thr Phe Asp Glu Thr
305                 310                 315                 320

Val Ser Thr Tyr Val Pro Leu Ala Gln Gln Val Glu Asp Phe His Lys
                325                 330                 335

Arg Thr Pro Asn Arg Tyr His Leu Arg Ser Lys Lys Asp Asp Ile Asn
            340                 345                 350

Leu Leu Pro Ser Lys Ser Ser Val Thr Lys Ile Cys Arg Asp Pro Gln
        355                 360                 365

Thr Pro Val Leu Gln Thr Lys His Arg Ala Arg Ala Val Thr Cys Lys
    370                 375                 380

Ser Thr Ala Glu Leu Glu Ala Glu Glu Leu Glu Lys Leu Gln Gln Tyr
385                 390                 395                 400

Lys Phe Lys Ala Arg Glu Leu Asp Pro Arg Ile Leu Glu Gly Gly Pro
                405                 410                 415

Ile Leu Pro Lys Lys Pro Pro Val Lys Pro Pro Thr Glu Pro Ile Gly
            420                 425                 430

Phe Asp Leu Glu Ile Glu Lys Arg Ile Gln Glu Arg Glu Ser Lys Lys
        435                 440                 445
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Lys Thr Glu Asp Glu His Phe Glu Phe His Ser Arg Pro Cys Pro Thr
    450                 455                 460

Lys Ile Leu Glu Asp Val Val Gly Val Pro Glu Lys Lys Val Leu Pro
465                 470                 475                 480

Ile Thr Val Pro Lys Ser Pro Ala Phe Ala Leu Lys Asn Arg Ile Arg
                485                 490                 495

Met Pro Thr Lys Glu Asp Glu Glu Glu Asp Glu Pro Val Val Ile Lys
            500                 505                 510

Ala Gln Pro Val Pro His Tyr Gly Val Pro Phe Lys Pro Gln Ile Pro
        515                 520                 525

Glu Ala Arg Thr Val Glu Ile Cys Pro Phe Ser Phe Asp Ser Arg Asp
    530                 535                 540

Lys Glu Arg Gln Leu Gln Lys Glu Lys Lys Ile Lys Glu Leu Gln Lys
545                 550                 555                 560

Gly Glu Val Pro Lys Phe Lys Ala Leu Pro Leu Pro His Phe Asp Thr
                565                 570                 575

Ile Asn Leu Pro Glu Lys Lys Val Lys Asn Val Thr Gln Ile Glu Pro
            580                 585                 590

Phe Cys Leu Glu Thr Asp Arg Arg Gly Ala Leu Lys Ala Gln Thr Trp
        595                 600                 605

Lys His Gln Leu Glu Glu Glu Leu Arg Gln Gln Lys Glu Ala Ala Cys
    610                 615                 620

Phe Lys Ala Arg Pro Asn Thr Val Ile Ser Gln Glu Pro Phe Val Pro
625                 630                 635                 640

Lys Lys Glu Lys Lys Ser Val Ala Glu Gly Leu Ser Gly Ser Leu Val
                645                 650                 655

Gln Glu Pro Phe Gln Leu Ala Thr Glu Lys Arg Ala Lys Glu Arg Gln
            660                 665                 670

Glu Leu Glu Lys Arg Met Ala Glu Val Glu Ala Gln Lys Ala Gln Gln
        675                 680                 685

Leu Glu Glu Ala Arg Leu Gln Glu Glu Glu Gln Lys Lys Glu Glu Leu
    690                 695                 700

Ala Arg Leu Arg Arg Glu Leu Val His Lys Ala Asn Pro Ile Arg Lys
705                 710                 715                 720
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Tyr Gln Gly Leu Glu Ile Lys Ser Ser Asp Gln Pro Leu Thr Val Pro
                725                 730                 735

Val Ser Pro Lys Phe Ser Thr Arg Phe His Cys
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<211> 1246

<212> DNA

<213> NM_001769 CD9

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<221> CDS

<222> (112)..(795)

<223>

<400> 35

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cgcgcccccc agtcccgcac ccgttcggcc caggctaagt tagccctcac c atg ccg      117
                                                         Met Pro
                                                         1

gtc aaa gga ggc acc aag tgc atc aaa tac ctg ctg ttc gga ttt aac      165
Val Lys Gly Gly Thr Lys Cys Ile Lys Tyr Leu Leu Phe Gly Phe Asn
        5                   10                  15

ttc atc ttc tgg ctt gcc ggg att gct gtc ctt gcc att gga cta tgg      213
Phe Ile Phe Trp Leu Ala Gly Ile Ala Val Leu Ala Ile Gly Leu Trp
    20                  25                  30

ctc cga ttc gac tct cag acc aag agc atc ttc gag caa gaa act aat      261
Leu Arg Phe Asp Ser Gln Thr Lys Ser Ile Phe Glu Gln Glu Thr Asn
35                  40                  45                  50

aat aat aat tcc agc ttc tac aca gga gtc tat att ctg atc gga gcc      309
Asn Asn Asn Ser Ser Phe Tyr Thr Gly Val Tyr Ile Leu Ile Gly Ala
                55                  60                  65

ggc gcc ctc atg atg ctg gtg ggc ttc ctg ggc tgc tgc ggg gct gtg      357
Gly Ala Leu Met Met Leu Val Gly Phe Leu Gly Cys Cys Gly Ala Val
            70                  75                  80

cag gag tcc cag tgc atg ctg gga ctg ttc ttc ggc ttc ctc ttg gtg      405
Gln Glu Ser Gln Cys Met Leu Gly Leu Phe Phe Gly Phe Leu Leu Val
        85                  90                  95

ata ttc gcc att gaa ata gct gcg gcc atc tgg gga tat tcc cac aag      453
Ile Phe Ala Ile Glu Ile Ala Ala Ala Ile Trp Gly Tyr Ser His Lys
    100                 105                 110

gat gag gtg att aag gaa gtc cag gag ttt tac aag gac acc tac aac      501
Asp Glu Val Ile Lys Glu Val Gln Glu Phe Tyr Lys Asp Thr Tyr Asn
115                 120                 125                 130

aag ctg aaa acc aag gat gag ccc cag cgg gaa acg ctg aaa gcc atc      549
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Lys Leu Lys Thr Lys Asp Glu Pro Gln Arg Glu Thr Leu Lys Ala Ile
135 140 145

cac tat gcg ttg aac tgc tgt ggt ttg gct ggg ggc gtg gaa cag ttt 597
His Tyr Ala Leu Asn Cys Cys Gly Leu Ala Gly Gly Val Glu Gln Phe
150 155 160

atc tca gac atc tgc ccc aag aag gac gta ctc gaa acc ttc acc gtg 645
Ile Ser Asp Ile Cys Pro Lys Lys Asp Val Leu Glu Thr Phe Thr Val
165 170 175

aag tcc tgt cct gat gcc atc aaa gag gtc ttc gac aat aaa ttc cac 693
Lys Ser Cys Pro Asp Ala Ile Lys Glu Val Phe Asp Asn Lys Phe His
180 185 190

atc atc ggc gca gtg ggc atc ggc att gcc gtg gtc atg ata ttt ggc 741
Ile Ile Gly Ala Val Gly Ile Gly Ile Ala Val Val Met Ile Phe Gly
195 200 205 210

atg atc ttc agt atg atc ttg tgc tgt gct atc cgc agg aac cgc gag 789
Met Ile Phe Ser Met Ile Leu Cys Cys Ala Ile Arg Arg Asn Arg Glu
215 220 225

atg gtc tagagtcagc ttacatccct gagcaggaaa gtttacccat gaagattggt 845
Met Val

gggatttttt gtttgtttgt tttgttttgt ttgttgtttg ttgtttgttt ttttgccact 905

aattttagta ttcattctgc attgctagat aaaagctgaa gttactttat gtttgtcttt 965

taatgcttca ttcaatattg acatttgtag ttgagcgggg ggtttggttt gctttggttt 1025

atattttttc agttgtttgt tttgcttgt tatattaagc agaaatcctg caatgaaagg 1085

tactatattt gctagactct agacaagata ttgtacataa aagaattttt ttgtctttaa 1145

atagatacaa atgtctatca actttaatca agttgtaact tatattgaag acaatttgat 1205

acataataaa aaattatgac aatgtcaaaa aaaaaaaaaa a 1246

<210> 36

<211> 228

<212> PRT

<213> NM_001769 CD9

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Phe Asn Phe Ile Phe Trp Leu Ala Gly Ile Ala Val Leu Ala Ile Gly
20 25 30

Leu Trp Leu Arg Phe Asp Ser Gln Thr Lys Ser Ile Phe Glu Gln Glu
35 40 45

Thr Asn Asn Asn Asn Ser Ser Phe Tyr Thr Gly Val Tyr Ile Leu Ile
50 55 60

Gly Ala Gly Ala Leu Met Met Leu Val Gly Phe Leu Gly Cys Cys Gly
65 70 75 80

Ala Val Gln Glu Ser Gln Cys Met Leu Gly Leu Phe Phe Gly Phe Leu
85 90 95

Leu Val Ile Phe Ala Ile Glu Ile Ala Ala Ala Ile Trp Gly Tyr Ser
100 105 110

His Lys Asp Glu Val Ile Lys Glu Val Gln Glu Phe Tyr Lys Asp Thr
115 120 125

Tyr Asn Lys Leu Lys Thr Lys Asp Glu Pro Gln Arg Glu Thr Leu Lys
130 135 140

Ala Ile His Tyr Ala Leu Asn Cys Cys Gly Leu Ala Gly Gly Val Glu
145 150 155 160

Gln Phe Ile Ser Asp Ile Cys Pro Lys Lys Asp Val Leu Glu Thr Phe
165 170 175

Thr Val Lys Ser Cys Pro Asp Ala Ile Lys Glu Val Phe Asp Asn Lys
180 185 190

Phe His Ile Ile Gly Ala Val Gly Ile Gly Ile Ala Val Val Met Ile
195 200 205

Phe Gly Met Ile Phe Ser Met Ile Leu Cys Cys Ala Ile Arg Arg Asn
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Arg Glu Met Val
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taacttcctt actctttctc tcaagaggag gcaagtggct gtggcggccg cagcagtggc    180

tgatcatcac tgaaaatacc aaagaaaaga actgagctgc ctccttcata tttttccat    240

tgaggattaa tttaccgtgc tttttcattt tctctacatc ctgcaaaagt ttttttctct    300

cctaagaaac aaactatgaa ctgattgttg aaaaaaagaa gtaaaaagtt ttagcacagc    360

ttctctgtct cttcgggaca agttagaaaa ttctgaagtg agccgaagca tagtaagtgc    420

tttctttctt tttaagctac ttctggggag ggaggaggct attgtaatgg taaatttcac    480

tccgagagga agaaagggtt gataatcaat caaaaatgag gtattccttt gagtatttgt    540

gattttctta ctatattgta agatgctttt aattttctct gtaaaatagg cagaaatggt    600

tttagtgtgt gtatgtgtga aataaaagct cagaaaagca atcttcagag cgccactgaa    660

ggaagttttg acgaacggag tagagatgta taccacttgg gggcttcagt gagaacccag    720

aattcctgga ggaggattta cattcagaaa tgttgaagtg aaaattcctt ctggttcagc    780

atcttggagt tcagcttgga agaacatttt acgtatggaa gaatttgctt ctccaaacct    840

ctcttttggc cattgtgtgt cctgaaggat gggacaactt gtgctgtaga agcactgctt    900

gcctgagttt gcttcaggca ttttaaattt aacttgaggg atcatgtgtt tggcatg      957

atg agg acc act gaa gac ttc cac aag cct agt gcc aca tta aac tct    1005
Met Arg Thr Thr Glu Asp Phe His Lys Pro Ser Ala Thr Leu Asn Ser
1               5                   10                  15

aac acg gcc acc aag gga agg tac att tat ctg gag gca ttc ctg gag    1053
Asn Thr Ala Thr Lys Gly Arg Tyr Ile Tyr Leu Glu Ala Phe Leu Glu
            20                  25                  30

gga gga gct ccc tgg ggt ttt act cta aag ggt ggc ctg gag cac gga    1101
Gly Gly Ala Pro Trp Gly Phe Thr Leu Lys Gly Gly Leu Glu His Gly
        35                  40                  45

gaa cca tta atc atc tct aag gtc gaa gaa ggg ggc aaa gca gac acc    1149
Glu Pro Leu Ile Ile Ser Lys Val Glu Glu Gly Gly Lys Ala Asp Thr
    50                  55                  60

ctg agc tcc aaa ctg cag gct ggg gat gag gtt gtg cac atc aat gag    1197
Leu Ser Ser Lys Leu Gln Ala Gly Asp Glu Val Val His Ile Asn Glu
65                  70                  75                  80

gtg act ctg agc agc tcc aga aag gag gca gtt tcc ctg gtg aaa gga    1245
Val Thr Leu Ser Ser Ser Arg Lys Glu Ala Val Ser Leu Val Lys Gly
                85                  90                  95

tcc tac aag acc ctc agg ctg gta gtg cgc aga gat gtg tgc aca gac    1293
Ser Tyr Lys Thr Leu Arg Leu Val Val Arg Arg Asp Val Cys Thr Asp
            100                 105                 110

cca ggc cat gca gat act ggt gcc tct aac ttc gtc agc cca gaa cac    1341
Pro Gly His Ala Asp Thr Gly Ala Ser Asn Phe Val Ser Pro Glu His
        115                 120                 125

ctc acc tct ggc ccc cag cac agg aaa gca gcg tgg tca gga ggg gtt    1389
Leu Thr Ser Gly Pro Gln His Arg Lys Ala Ala Trp Ser Gly Gly Val
    130                 135                 140

aaa ctt cgg ctg aag cac agg tct agt gag cct gca ggc cga cct cac    1437
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Lys Leu Arg Leu Lys His Arg Ser Ser Glu Pro Ala Gly Arg Pro His
145                 150                 155                 160

tcg tgg cac aca act aaa tct ggg gag aag caa ccc gat gcc agc atg      1485
Ser Trp His Thr Thr Lys Ser Gly Glu Lys Gln Pro Asp Ala Ser Met
                165                 170                 175

atg cag ata tct cag ggt atg atc ggc cct cct tgg cac caa agc tac      1533
Met Gln Ile Ser Gln Gly Met Ile Gly Pro Pro Trp His Gln Ser Tyr
            180                 185                 190

cat tcc agc tcc tct act agt gac ctc tcc aac tat gac cat gct tat      1581
His Ser Ser Ser Ser Thr Ser Asp Leu Ser Asn Tyr Asp His Ala Tyr
        195                 200                 205

cta agg cgg agc cct gac cag tgc agc tcc cag ggg agc atg gag agc      1629
Leu Arg Arg Ser Pro Asp Gln Cys Ser Ser Gln Gly Ser Met Glu Ser
    210                 215                 220

ctg gag ccc agt ggg gca tac cca ccc tgt cat ctt tcc cct gcc aag      1677
Leu Glu Pro Ser Gly Ala Tyr Pro Pro Cys His Leu Ser Pro Ala Lys
225                 230                 235                 240

tcc acc ggc agc att gac cag ctc agc cac ttc cat aac aag aga gac      1725
Ser Thr Gly Ser Ile Asp Gln Leu Ser His Phe His Asn Lys Arg Asp
                245                 250                 255

tcg gct tac agc tct ttc tcc acc agt tct agc atc cta gag tat cca      1773
Ser Ala Tyr Ser Ser Phe Ser Thr Ser Ser Ser Ile Leu Glu Tyr Pro
            260                 265                 270

cac cct ggc atc tct gcc cgg gag cgt tca ggc tcc atg gac aat act      1821
His Pro Gly Ile Ser Ala Arg Glu Arg Ser Gly Ser Met Asp Asn Thr
        275                 280                 285

tct gct cga ggt ggc ctc ctc gaa ggg atg agg cag gca gat att cgc      1869
Ser Ala Arg Gly Gly Leu Leu Glu Gly Met Arg Gln Ala Asp Ile Arg
    290                 295                 300

tat gtc aag aca gtc tat gac acc cgg agg gga gtc tca gca gag tat      1917
Tyr Val Lys Thr Val Tyr Asp Thr Arg Arg Gly Val Ser Ala Glu Tyr
305                 310                 315                 320

gag gtg aac tct tca gcc ctg ctg ctt caa ggt agg gag gcc cga gcc      1965
Glu Val Asn Ser Ser Ala Leu Leu Leu Gln Gly Arg Glu Ala Arg Ala
                325                 330                 335

tca gca aat ggt cag ggc tat gat aaa tgg tct aat att cct cgg ggc      2013
Ser Ala Asn Gly Gln Gly Tyr Asp Lys Trp Ser Asn Ile Pro Arg Gly
            340                 345                 350

aag gga gtg cca ccc cca tcc tgg agc cag cag tgc ccc agt tcc ttg      2061
Lys Gly Val Pro Pro Pro Ser Trp Ser Gln Gln Cys Pro Ser Ser Leu
        355                 360                 365

gag act gcc acg gac aac ctt cct cct aag gtg ggt gca ccc ctg cct      2109
Glu Thr Ala Thr Asp Asn Leu Pro Pro Lys Val Gly Ala Pro Leu Pro
    370                 375                 380

cca gct cgg agt gac agt tac gca gca ttt cgg cac cgt gag cgg ccc      2157
Pro Ala Arg Ser Asp Ser Tyr Ala Ala Phe Arg His Arg Glu Arg Pro
385                 390                 395                 400

agc tcc tgg tct agc ctt gat cag aaa cgg ctc tgc cgg cct cag gca      2205
Ser Ser Trp Ser Ser Leu Asp Gln Lys Arg Leu Cys Arg Pro Gln Ala
                405                 410                 415

aac tct tta ggc tcc ctg aag tct cca ttc ata gag gag cag ctg cat      2253
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Asn Ser Leu Gly Ser Leu Lys Ser Pro Phe Ile Glu Glu Gln Leu His
420 425 430

act gtg ctg gag aag agt cca gag aac agc ccc cca gtg aag ccc aag 2301
Thr Val Leu Glu Lys Ser Pro Glu Asn Ser Pro Pro Val Lys Pro Lys
435 440 445

cat aac tat acc cag aag gcc caa cct ggc caa cct ctg ctg ccg acc 2349
His Asn Tyr Thr Gln Lys Ala Gln Pro Gly Gln Pro Leu Leu Pro Thr
450 455 460

agc atc tac gcg gta cct tcc ctg gag cca cac ttt gcc cag gtg cct 2397
Ser Ile Tyr Ala Val Pro Ser Leu Glu Pro His Phe Ala Gln Val Pro
465 470 475 480

cag cct tct gtg agt agc aac ggt atg ctc tac cct gca ctg gcc aag 2445
Gln Pro Ser Val Ser Ser Asn Gly Met Leu Tyr Pro Ala Leu Ala Lys
485 490 495

gag agt gga tac ata gcc cct cag gga gca tgc aac aag atg gct acc 2493
Glu Ser Gly Tyr Ile Ala Pro Gln Gly Ala Cys Asn Lys Met Ala Thr
500 505 510

att gat gag aat ggg aac cag aat gga tct ggc agg cct ggg ttt gcc 2541
Ile Asp Glu Asn Gly Asn Gln Asn Gly Ser Gly Arg Pro Gly Phe Ala
515 520 525

ttc tgc cag ccc tta gaa cat gac ttg ctg tcc cca gtg gag aag aaa 2589
Phe Cys Gln Pro Leu Glu His Asp Leu Leu Ser Pro Val Glu Lys Lys
530 535 540

cca gaa gct aca gcc aag tat gtc ccc tcc aaa gtc cat ttc tgt tca 2637
Pro Glu Ala Thr Ala Lys Tyr Val Pro Ser Lys Val His Phe Cys Ser
545 550 555 560

gtg cct gaa aat gag gag gat gcc tcc ctg aag aga cat ctc aca cct 2685
Val Pro Glu Asn Glu Glu Asp Ala Ser Leu Lys Arg His Leu Thr Pro
565 570 575

ccc caa ggc aac agc cca cat tcc aat gag aga aag agc acc cac agt 2733
Pro Gln Gly Asn Ser Pro His Ser Asn Glu Arg Lys Ser Thr His Ser
580 585 590

aac aaa cca tct tct cat ccc cac agc ctc aaa tgc cct cag gct cag 2781
Asn Lys Pro Ser Ser His Pro His Ser Leu Lys Cys Pro Gln Ala Gln
595 600 605

gcc tgg caa gcg ggt gaa gac aag aga tct tcc agg ctc tca gag ccc 2829
Ala Trp Gln Ala Gly Glu Asp Lys Arg Ser Ser Arg Leu Ser Glu Pro
610 615 620

tgg gag ggc gat ttc cag gaa gac cac aat gcc aac ctc tgg agg agg 2877
Trp Glu Gly Asp Phe Gln Glu Asp His Asn Ala Asn Leu Trp Arg Arg
625 630 635 640

ctg gag aga gaa ggc cta ggc cag agc ctg tca ggc aac ttt ggc aag 2925
Leu Glu Arg Glu Gly Leu Gly Gln Ser Leu Ser Gly Asn Phe Gly Lys
645 650 655

acc aag tca gcc ttc tca tct ctc cag aac att cct gag agt ctg aga 2973
Thr Lys Ser Ala Phe Ser Ser Leu Gln Asn Ile Pro Glu Ser Leu Arg
660 665 670

aga cac agc agc ctg gag cta ggc cgg gga acc cag gag ggt tac ccc 3021
Arg His Ser Ser Leu Glu Leu Gly Arg Gly Thr Gln Glu Gly Tyr Pro
675 680 685

ggg ggc agg ccc acc tgt gca gtc aac acc aag gca gaa gac cct ggg 3069

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Gly Gly Arg Pro Thr Cys Ala Val Asn Thr Lys Ala Glu Asp Pro Gly
    690                 695                 700

agg aaa gcc gct cct gac ctc ggg agc cat ctg gac cgg cag gtt tcc        3117
Arg Lys Ala Ala Pro Asp Leu Gly Ser His Leu Asp Arg Gln Val Ser
705                 710                 715                 720

tac ccg cgg ccc gag ggg agg acc ggt gcc tcg gct tct ttc aac agc        3165
Tyr Pro Arg Pro Glu Gly Arg Thr Gly Ala Ser Ala Ser Phe Asn Ser
                725                 730                 735

aca gac cca agt ccc gaa gag ccg cct gcc ccc tcg cac ccg cac aca        3213
Thr Asp Pro Ser Pro Glu Glu Pro Pro Ala Pro Ser His Pro His Thr
            740                 745                 750

tcc agt ctg ggc cgg agg ggg ccc ggc cca ggc agc gcc tcg gct ctt        3261
Ser Ser Leu Gly Arg Arg Gly Pro Gly Pro Gly Ser Ala Ser Ala Leu
        755                 760                 765

cag ggc ttt cag tac ggg aag ccc cac tgc tcg gtg ctg gag aag gtc        3309
Gln Gly Phe Gln Tyr Gly Lys Pro His Cys Ser Val Leu Glu Lys Val
    770                 775                 780

tcc aaa ttc gag cag cga gag caa ggg agc cag aga ccg agt gtg ggc        3357
Ser Lys Phe Glu Gln Arg Glu Gln Gly Ser Gln Arg Pro Ser Val Gly
785                 790                 795                 800

ggc tct ggt ttt ggc cat aac tat agg ccc cac agg acc gtc tca act        3405
Gly Ser Gly Phe Gly His Asn Tyr Arg Pro His Arg Thr Val Ser Thr
                805                 810                 815

tcc agt act tct ggg aat gac ttc gag gag aca aaa gca cac att cgt        3453
Ser Ser Thr Ser Gly Asn Asp Phe Glu Glu Thr Lys Ala His Ile Arg
            820                 825                 830

ttc tct gag tca gct gaa ccc cta ggc aac ggg gag cag cac ttc aaa        3501
Phe Ser Glu Ser Ala Glu Pro Leu Gly Asn Gly Glu Gln His Phe Lys
        835                 840                 845

aac ggg gag ctg aag ttg gaa gag gct tcc cgg cag ccc tgc ggt cag        3549
Asn Gly Glu Leu Lys Leu Glu Glu Ala Ser Arg Gln Pro Cys Gly Gln
    850                 855                 860

cag ctg agc gga gga gcg tcg gac agc ggc cgt ggc ccc cag agg ccg        3597
Gln Leu Ser Gly Gly Ala Ser Asp Ser Gly Arg Gly Pro Gln Arg Pro
865                 870                 875                 880

gac gct cgg ctc ctc cgt agc cag agc acc ttc cag ctc tcc agc gag        3645
Asp Ala Arg Leu Leu Arg Ser Gln Ser Thr Phe Gln Leu Ser Ser Glu
                885                 890                 895

cca gag agg gag ccc gag tgg cgg gac agg ccc ggc tcg ccc gaa tcg        3693
Pro Glu Arg Glu Pro Glu Trp Arg Asp Arg Pro Gly Ser Pro Glu Ser
            900                 905                 910

ccc ctg ctg gat gcc ccc ttc agc cgc gcc tac cgg aac agc atc aag        3741
Pro Leu Leu Asp Ala Pro Phe Ser Arg Ala Tyr Arg Asn Ser Ile Lys
        915                 920                 925

gac gca cag tcc cgt gtc ttg ggg gcc acc tcc ttt cga cgt cga gac        3789
Asp Ala Gln Ser Arg Val Leu Gly Ala Thr Ser Phe Arg Arg Arg Asp
    930                 935                 940

ctg gag ctg ggg gcg ccc gtg gcg tcg agg tcc tgg cgg cca cgg cct        3837
Leu Glu Leu Gly Ala Pro Val Ala Ser Arg Ser Trp Arg Pro Arg Pro
945                 950                 955                 960

tcc tcg gcc cac gtg ggg ctg cgg agc ccc gag gcg tcg gcc tcc gcc        3885
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Ser Ser Ala His Val Gly Leu Arg Ser Pro Glu Ala Ser Ala Ser Ala
                965                 970                 975

tcc ccg cac acg ccc cgg gag cgg cac agc gtg acc cct gct gag ggc     3933
Ser Pro His Thr Pro Arg Glu Arg His Ser Val Thr Pro Ala Glu Gly
            980                 985                 990

gac ctg gcc agg ccc gtg ccc cct  gcc gcc cgg aga ggt  gct cgc cgg   3981
Asp Leu Ala Arg Pro Val Pro Pro  Ala Ala Arg Arg Gly  Ala Arg Arg
        995                 1000                1005

cgc ctg  act ccc gag cag aag  aag cgc tcc tac tcg  gag ccc gag      4026
Arg Leu  Thr Pro Glu Gln Lys  Lys Arg Ser Tyr Ser  Glu Pro Glu
    1010                1015                1020

aag atg  aac gag gtg ggg atc  gtg gag gag gcc gaa  ccg gca ccc      4071
Lys Met  Asn Glu Val Gly Ile  Val Glu Glu Ala Glu  Pro Ala Pro
    1025                1030                1035

ctg ggc  ccg cag aga aat ggg  atg cgt ttc ccg gag  agc agc gtg      4116
Leu Gly  Pro Gln Arg Asn Gly  Met Arg Phe Pro Glu  Ser Ser Val
    1040                1045                1050

gcc gac  cgg cgc cgt ctc ttc  gag cgc gat ggc aag  gcc tgc tcc      4161
Ala Asp  Arg Arg Arg Leu Phe  Glu Arg Asp Gly Lys  Ala Cys Ser
    1055                1060                1065

acg ctc  agc ctg tcg ggg ccc  gag ctg aag cag ttc  cag cag agc      4206
Thr Leu  Ser Leu Ser Gly Pro  Glu Leu Lys Gln Phe  Gln Gln Ser
    1070                1075                1080

gcc ctg  gcg gac tac atc cag  cgc aag acc ggc aag  cgg cct acc      4251
Ala Leu  Ala Asp Tyr Ile Gln  Arg Lys Thr Gly Lys  Arg Pro Thr
    1085                1090                1095

tcc gcc  gcc ggc tgc agc ctc  cag gag ccc ggg cca  ctg cgt gag      4296
Ser Ala  Ala Gly Cys Ser Leu  Gln Glu Pro Gly Pro  Leu Arg Glu
    1100                1105                1110

cgc gcc  cag agt gcc tac ctc  cag ccc ggc ccc gcg  gcg ctc gaa      4341
Arg Ala  Gln Ser Ala Tyr Leu  Gln Pro Gly Pro Ala  Ala Leu Glu
    1115                1120                1125

ggc tcc  ggc ctc gcc tcg gcc  tcc agc ttg agc tca  ctg cgg gag      4386
Gly Ser  Gly Leu Ala Ser Ala  Ser Ser Leu Ser Ser  Leu Arg Glu
    1130                1135                1140

ccc agc  ctg cag ccc cgc agg  gag gcc acg ctc ctg  ccg gcc aca      4431
Pro Ser  Leu Gln Pro Arg Arg  Glu Ala Thr Leu Leu  Pro Ala Thr
    1145                1150                1155

gtt gca  gaa acc cag cag gct  ccc cga gat cgc agc  agc tcc ttc      4476
Val Ala  Glu Thr Gln Gln Ala  Pro Arg Asp Arg Ser  Ser Ser Phe
    1160                1165                1170

gcc ggt  ggc cgc cgc ctc ggg  gaa cgg cga cgc ggg  gac ctg ctt      4521
Ala Gly  Gly Arg Arg Leu Gly  Glu Arg Arg Arg Gly  Asp Leu Leu
    1175                1180                1185

agc gga  gca aac ggt gga aca  agg ggc acc cag aga  ggg gat gag      4566
Ser Gly  Ala Asn Gly Gly Thr  Arg Gly Thr Gln Arg  Gly Asp Glu
    1190                1195                1200

acc ccc  agg gag cca tcc tcc  tgg ggg gcc agg gcc  ggg aag tcc      4611
Thr Pro  Arg Glu Pro Ser Ser  Trp Gly Ala Arg Ala  Gly Lys Ser
    1205                1210                1215

atg tcg  gcc gag gac ctg ctg  gaa cgc tcg gac gtc  ctt gcg ggc      4656
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Met Ser  Ala Glu Asp Leu Leu  Glu Arg Ser Asp Val  Leu Ala Gly
    1220                 1225                 1230

cct gtc  cat gtg agg tcc agg  tca tct ccc gcc acc  gca gac aag       4701
Pro Val  His Val Arg Ser Arg  Ser Ser Pro Ala Thr  Ala Asp Lys
    1235                 1240                 1245

cgc cag  gat gtg ctt ttg ggg  caa gac agt ggc ttt  ggt ctt gtg       4746
Arg Gln  Asp Val Leu Leu Gly  Gln Asp Ser Gly Phe  Gly Leu Val
    1250                 1255                 1260

aag gat  cca tgt tat ttg gct  ggt cct gga tct agg  tca ctc agt       4791
Lys Asp  Pro Cys Tyr Leu Ala  Gly Pro Gly Ser Arg  Ser Leu Ser
    1265                 1270                 1275

tgt tca  gaa aga ggc caa gaa  gag atg ctg ctg ctc  ttc cac cat       4836
Cys Ser  Glu Arg Gly Gln Glu  Glu Met Leu Leu Leu  Phe His His
    1280                 1285                 1290

ctc acc  cct cgt tgg ggt ggt  tca ggc tgc aaa gcc  att ggt gat       4881
Leu Thr  Pro Arg Trp Gly Gly  Ser Gly Cys Lys Ala  Ile Gly Asp
    1295                 1300                 1305

tcc tcc  gtt cct agt gaa tgt  cct gga acc ctg gac  cat cag agg       4926
Ser Ser  Val Pro Ser Glu Cys  Pro Gly Thr Leu Asp  His Gln Arg
    1310                 1315                 1320

caa gcc  agt agg aca ccc tgc  ccc agg cca cca ctg  gca gga acg       4971
Gln Ala  Ser Arg Thr Pro Cys  Pro Arg Pro Pro Leu  Ala Gly Thr
    1325                 1330                 1335

caa ggg  ctg gtc aca gac acc  agg gct gca ccc ctg  acc cca att       5016
Gln Gly  Leu Val Thr Asp Thr  Arg Ala Ala Pro Leu  Thr Pro Ile
    1340                 1345                 1350

ggc acc  cct ctg cct tca gcc  att ccc tct ggc tac  tgc tca cag       5061
Gly Thr  Pro Leu Pro Ser Ala  Ile Pro Ser Gly Tyr  Cys Ser Gln
    1355                 1360                 1365

gac ggt  cag aca ggg cga cag  cct ctc ccg ccc tac  acc cct gcc       5106
Asp Gly  Gln Thr Gly Arg Gln  Pro Leu Pro Pro Tyr  Thr Pro Ala
    1370                 1375                 1380

atg atg  cac aga agc aat ggt  cac acc ctg acc cag  cct ccc ggt       5151
Met Met  His Arg Ser Asn Gly  His Thr Leu Thr Gln  Pro Pro Gly
    1385                 1390                 1395

cca aga  ggc tgt gag ggc gat  ggc cca gag cat ggg  gta gaa gag       5196
Pro Arg  Gly Cys Glu Gly Asp  Gly Pro Glu His Gly  Val Glu Glu
    1400                 1405                 1410

gga acg  agg aag agg gtc tcg  ctg cct cag tgg cca  cct cct tct       5241
Gly Thr  Arg Lys Arg Val Ser  Leu Pro Gln Trp Pro  Pro Pro Ser
    1415                 1420                 1425

cga gca  aag tgg gcc cac gca  gcc aga gag gac agc  ctt cct gag       5286
Arg Ala  Lys Trp Ala His Ala  Ala Arg Glu Asp Ser  Leu Pro Glu
    1430                 1435                 1440

gaa tcc  tca gcc cct gat ttt  gca aac ctg aag cac  tat caa aaa       5331
Glu Ser  Ser Ala Pro Asp Phe  Ala Asn Leu Lys His  Tyr Gln Lys
    1445                 1450                 1455

cag cag  agt ctt cca agt tta  tgc agc act tct gac  cca gac aca       5376
Gln Gln  Ser Leu Pro Ser Leu  Cys Ser Thr Ser Asp  Pro Asp Thr
    1460                 1465                 1470

cct ctt  ggg gcc ccg agc act  cca ggg agg atc tcc  ctc cga ata       5421
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Pro Leu  Gly Ala Pro Ser Thr  Pro Gly Arg Ile Ser  Leu Arg Ile
    1475                 1480                 1485

tct gag  tct gtc ctg cgg gac  tcc ccg cca cct cat  gag gat tat      5466
Ser Glu  Ser Val Leu Arg Asp  Ser Pro Pro Pro His  Glu Asp Tyr
    1490                 1495                 1500

gaa gac  gaa gtg ttt gtg agg  gat ccg cac ccc aag  gcc acg tcc      5511
Glu Asp  Glu Val Phe Val Arg  Asp Pro His Pro Lys  Ala Thr Ser
    1505                 1510                 1515

agc ccc  aca ttt gaa cct ctt  ccc cca ccc cca cct  cct cca ccg      5556
Ser Pro  Thr Phe Glu Pro Leu  Pro Pro Pro Pro Pro  Pro Pro Pro
    1520                 1525                 1530

agt cag  gaa acc ccg gtg tat  agc atg gat gac ttc  cct cca cct      5601
Ser Gln  Glu Thr Pro Val Tyr  Ser Met Asp Asp Phe  Pro Pro Pro
    1535                 1540                 1545

cct ccc  cac act gta tgt gag  gcg cag ctg gac agt  gag gat ccc      5646
Pro Pro  His Thr Val Cys Glu  Ala Gln Leu Asp Ser  Glu Asp Pro
    1550                 1555                 1560

gag ggg  cca cgc ccc agc ttc  aac aaa ctt tct aaa  gtg aca att      5691
Glu Gly  Pro Arg Pro Ser Phe  Asn Lys Leu Ser Lys  Val Thr Ile
    1565                 1570                 1575

gca agg  gaa agg cac atg cct  ggt gca gcc cat gtg  gta ggt agt      5736
Ala Arg  Glu Arg His Met Pro  Gly Ala Ala His Val  Val Gly Ser
    1580                 1585                 1590

cag aca  ctg gct tcc aga ctc  caa act tct atc aag  ggt tca gag      5781
Gln Thr  Leu Ala Ser Arg Leu  Gln Thr Ser Ile Lys  Gly Ser Glu
    1595                 1600                 1605

gct gag  tcc aca cca ccc tcc  ttc atg agc gtt cac  gcc caa ctt      5826
Ala Glu  Ser Thr Pro Pro Ser  Phe Met Ser Val His  Ala Gln Leu
    1610                 1615                 1620

gct ggg  tct ctt ggt ggg cag  cca gca ccc atc cag  act caa agc      5871
Ala Gly  Ser Leu Gly Gly Gln  Pro Ala Pro Ile Gln  Thr Gln Ser
    1625                 1630                 1635

ctc agc  cat gat cca gtc agt  gga act cag ggt tta  gaa aag aaa      5916
Leu Ser  His Asp Pro Val Ser  Gly Thr Gln Gly Leu  Glu Lys Lys
    1640                 1645                 1650

gtc agt  cct gat cct cag aag  agt tca gaa gac atc  aga aca gag      5961
Val Ser  Pro Asp Pro Gln Lys  Ser Ser Glu Asp Ile  Arg Thr Glu
    1655                 1660                 1665

gct ttg  gcc aag gaa att gtc  cac caa gac aaa tct  cta gca gac      6006
Ala Leu  Ala Lys Glu Ile Val  His Gln Asp Lys Ser  Leu Ala Asp
    1670                 1675                 1680

att ttg  gat cca gac tcc agg  ctg aag aca aca atg  gac ctg atg      6051
Ile Leu  Asp Pro Asp Ser Arg  Leu Lys Thr Thr Met  Asp Leu Met
    1685                 1690                 1695

gaa ggt  ttg ttt ccc cga gat  gtg aac ttg ctg aag  gaa aac agt      6096
Glu Gly  Leu Phe Pro Arg Asp  Val Asn Leu Leu Lys  Glu Asn Ser
    1700                 1705                 1710

gta aag  agg aag gcc ata cag  aga act gtc agc tct  tca gga tgt      6141
Val Lys  Arg Lys Ala Ile Gln  Arg Thr Val Ser Ser  Ser Gly Cys
    1715                 1720                 1725

gaa ggc  aag agg aat gaa gac  aag gaa gca gtg agc  atg ttg gtt      6186
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Glu Gly Lys Arg Asn Glu Asp Lys Glu Ala Val Ser Met Leu Val
1730 1735 1740

aac tgc cct gcc tac tac agt gtg tct gct ccc aag gct gag cta 6231
Asn Cys Pro Ala Tyr Tyr Ser Val Ser Ala Pro Lys Ala Glu Leu
1745 1750 1755

ctg aac aaa atc aaa gag atg cca gca gaa gtg aat gag gaa gag 6276
Leu Asn Lys Ile Lys Glu Met Pro Ala Glu Val Asn Glu Glu Glu
1760 1765 1770

gaa cag gca gat gtc aat gaa aag aag gct gag ctc att gga agt 6321
Glu Gln Ala Asp Val Asn Glu Lys Lys Ala Glu Leu Ile Gly Ser
1775 1780 1785

ctc acc cac aag ctg gag acc ctc cag gag gcg aag ggg agc ctg 6366
Leu Thr His Lys Leu Glu Thr Leu Gln Glu Ala Lys Gly Ser Leu
1790 1795 1800

ctc acg gac atc aag ctc aac aac gcc ctg gga gaa gag gtg gag 6411
Leu Thr Asp Ile Lys Leu Asn Asn Ala Leu Gly Glu Glu Val Glu
1805 1810 1815

gct ctg atc agc gag ctc tgc aag ccc aat gag ttt gac aag tat 6456
Ala Leu Ile Ser Glu Leu Cys Lys Pro Asn Glu Phe Asp Lys Tyr
1820 1825 1830

agg atg ttc ata ggg gat ttg gac aag gtg gtc aac ctg ctg ctc 6501
Arg Met Phe Ile Gly Asp Leu Asp Lys Val Val Asn Leu Leu Leu
1835 1840 1845

tcc ctc tcg ggg cgt cta gcc cgt gtt gag aat gtc ctt agc ggc 6546
Ser Leu Ser Gly Arg Leu Ala Arg Val Glu Asn Val Leu Ser Gly
1850 1855 1860

ctt ggt gaa gat gcc agt aat gaa gaa agg agc tct ctt tac gag 6591
Leu Gly Glu Asp Ala Ser Asn Glu Glu Arg Ser Ser Leu Tyr Glu
1865 1870 1875

aaa agg aag atc ctg gct ggt cag cat gag gat gcc cgg gag ctg 6636
Lys Arg Lys Ile Leu Ala Gly Gln His Glu Asp Ala Arg Glu Leu
1880 1885 1890

aag gag aac ctg gat cgc agg gag cga gta gtg ctg ggc atc ttg 6681
Lys Glu Asn Leu Asp Arg Arg Glu Arg Val Val Leu Gly Ile Leu
1895 1900 1905

gcc aat tac ctt tca gag gag cag ctc cag gac tac cag cac ttc 6726
Ala Asn Tyr Leu Ser Glu Glu Gln Leu Gln Asp Tyr Gln His Phe
1910 1915 1920

gtg aaa atg aag tcc acg ctc ctc att gag caa cgg aag ctg gat 6771
Val Lys Met Lys Ser Thr Leu Leu Ile Glu Gln Arg Lys Leu Asp
1925 1930 1935

gac aag atc aag ctg ggc cag gag cag gtc aag tgt ctg ctg gag 6816
Asp Lys Ile Lys Leu Gly Gln Glu Gln Val Lys Cys Leu Leu Glu
1940 1945 1950

agc ctg ccc tca gat ttc att ccc aag gct ggg gcc ctg gct ctg 6861
Ser Leu Pro Ser Asp Phe Ile Pro Lys Ala Gly Ala Leu Ala Leu
1955 1960 1965

ccc cca aac ctc acg agt gag ccc att cct gct ggg ggc tgt act 6906
Pro Pro Asn Leu Thr Ser Glu Pro Ile Pro Ala Gly Gly Cys Thr
1970 1975 1980

ttc agt ggt att ttc cca aca tta acc tct cca ctt taacctcttc 6952

Phe Ser Gly Ile Phe Pro Thr Leu Thr Ser Pro Leu
1985 1990 1995

taaaataccc aaccaaaaga tcactgtttc tctcaacact atttaatctg aaaaatgttt 7012

cagtacaaac cactgtttga actatctggg ttattggtgt ttgttcctga tgaaaggaaa 7072

aaaattctct ccaggaggaa gcctttttcc ttcttgccct tcctgattga tcttctgaga 7132

gctcgaatgc tgctggacac gtacccctttt ctattattac tttgtagtag aaagaaagtt 7192

aatgaaactg agaactgatt ggagggtgtt tgatcattta gtttttaaca ggctgaggca 7252

acatggatca gtgtgtgtcc ccctcaggaa tgtatccaca gtggccttcc ttgctggtgg 7312

gcagtgtatc ctgatggcag ggtacaagta ccattaatga agggtctgca acataaagcc 7372

ttaaaaagac acacactaag aaaactgtaa aaccttgaac attgttattt atatttttta 7432

aaatggaaaa gatcactatg tttgttgtgc taaccactta tttgattctg ttttgtggtg 7492

gacatagatg attacgtttg agctttgtat tttgtgaaaa ccttaatgaa atgaattcca 7552

aagat 7557

<210> 38

<211> 1995

<212> PRT

<213> NM_020859 ShrmL, Shroom-related protein

<400> 38

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35 40 45

Glu Pro Leu Ile Ile Ser Lys Val Glu Glu Gly Gly Lys Ala Asp Thr
50 55 60

Leu Ser Ser Lys Leu Gln Ala Gly Asp Glu Val Val His Ile Asn Glu
65 70 75 80

Val Thr Leu Ser Ser Ser Arg Lys Glu Ala Val Ser Leu Val Lys Gly
85 90 95

Ser Tyr Lys Thr Leu Arg Leu Val Val Arg Arg Asp Val Cys Thr Asp
100 105 110

Pro Gly His Ala Asp Thr Gly Ala Ser Asn Phe Val Ser Pro Glu His
115 120 125

Leu Thr Ser Gly Pro Gln His Arg Lys Ala Ala Trp Ser Gly Gly Val
130 135 140

Lys Leu Arg Leu Lys His Arg Ser Ser Glu Pro Ala Gly Arg Pro His
145 150 155 160

Ser Trp His Thr Thr Lys Ser Gly Glu Lys Gln Pro Asp Ala Ser Met
165 170 175

Met Gln Ile Ser Gln Gly Met Ile Gly Pro Pro Trp His Gln Ser Tyr
180 185 190

His Ser Ser Ser Ser Thr Ser Asp Leu Ser Asn Tyr Asp His Ala Tyr
195 200 205

Leu Arg Arg Ser Pro Asp Gln Cys Ser Ser Gln Gly Ser Met Glu Ser
210 215 220

Leu Glu Pro Ser Gly Ala Tyr Pro Pro Cys His Leu Ser Pro Ala Lys
225 230 235 240

Ser Thr Gly Ser Ile Asp Gln Leu Ser His Phe His Asn Lys Arg Asp
245 250 255

Ser Ala Tyr Ser Ser Phe Ser Thr Ser Ser Ser Ile Leu Glu Tyr Pro
260 265 270

His Pro Gly Ile Ser Ala Arg Glu Arg Ser Gly Ser Met Asp Asn Thr
275 280 285

Ser Ala Arg Gly Gly Leu Leu Glu Gly Met Arg Gln Ala Asp Ile Arg
290 295 300

Tyr Val Lys Thr Val Tyr Asp Thr Arg Arg Gly Val Ser Ala Glu Tyr
305 310 315 320

Glu Val Asn Ser Ser Ala Leu Leu Leu Gln Gly Arg Glu Ala Arg Ala
325 330 335

Ser Ala Asn Gly Gln Gly Tyr Asp Lys Trp Ser Asn Ile Pro Arg Gly
340 345 350

Lys Gly Val Pro Pro Pro Ser Trp Ser Gln Gln Cys Pro Ser Ser Leu
355 360 365

Glu Thr Ala Thr Asp Asn Leu Pro Pro Lys Val Gly Ala Pro Leu Pro
370 375 380

Pro Ala Arg Ser Asp Ser Tyr Ala Ala Phe Arg His Arg Glu Arg Pro
385 390 395 400

Ser Ser Trp Ser Ser Leu Asp Gln Lys Arg Leu Cys Arg Pro Gln Ala
405 410 415

Asn Ser Leu Gly Ser Leu Lys Ser Pro Phe Ile Glu Glu Gln Leu His
420 425 430

Thr Val Leu Glu Lys Ser Pro Glu Asn Ser Pro Pro Val Lys Pro Lys
435 440 445

His Asn Tyr Thr Gln Lys Ala Gln Pro Gly Gln Pro Leu Leu Pro Thr
450 455 460

Ser Ile Tyr Ala Val Pro Ser Leu Glu Pro His Phe Ala Gln Val Pro
465 470 475 480

Gln Pro Ser Val Ser Ser Asn Gly Met Leu Tyr Pro Ala Leu Ala Lys
485 490 495

Glu Ser Gly Tyr Ile Ala Pro Gln Gly Ala Cys Asn Lys Met Ala Thr
500 505 510

Ile Asp Glu Asn Gly Asn Gln Asn Gly Ser Gly Arg Pro Gly Phe Ala
515 520 525

Phe Cys Gln Pro Leu Glu His Asp Leu Leu Ser Pro Val Glu Lys Lys
530 535 540

Pro Glu Ala Thr Ala Lys Tyr Val Pro Ser Lys Val His Phe Cys Ser
545 550 555 560

Val Pro Glu Asn Glu Glu Asp Ala Ser Leu Lys Arg His Leu Thr Pro
565 570 575

Pro Gln Gly Asn Ser Pro His Ser Asn Glu Arg Lys Ser Thr His Ser
580 585 590

Asn Lys Pro Ser Ser His Pro His Ser Leu Lys Cys Pro Gln Ala Gln
595 600 605

Ala Trp Gln Ala Gly Glu Asp Lys Arg Ser Ser Arg Leu Ser Glu Pro
610 615 620

Trp Glu Gly Asp Phe Gln Glu Asp His Asn Ala Asn Leu Trp Arg Arg
625 630 635 640

Leu Glu Arg Glu Gly Leu Gly Gln Ser Leu Ser Gly Asn Phe Gly Lys
645 650 655

Thr Lys Ser Ala Phe Ser Ser Leu Gln Asn Ile Pro Glu Ser Leu Arg
660 665 670

Arg His Ser Ser Leu Glu Leu Gly Arg Gly Thr Gln Glu Gly Tyr Pro
675 680 685

Gly Gly Arg Pro Thr Cys Ala Val Asn Thr Lys Ala Glu Asp Pro Gly
690 695 700

Arg Lys Ala Ala Pro Asp Leu Gly Ser His Leu Asp Arg Gln Val Ser
705 710 715 720

Tyr Pro Arg Pro Glu Gly Arg Thr Gly Ala Ser Ala Ser Phe Asn Ser
725 730 735

Thr Asp Pro Ser Pro Glu Glu Pro Pro Ala Pro Ser His Pro His Thr
740 745 750

Ser Ser Leu Gly Arg Arg Gly Pro Gly Pro Gly Ser Ala Ser Ala Leu
755 760 765

Gln Gly Phe Gln Tyr Gly Lys Pro His Cys Ser Val Leu Glu Lys Val
770 775 780

Ser Lys Phe Glu Gln Arg Glu Gln Gly Ser Gln Arg Pro Ser Val Gly
785 790 795 800

Gly Ser Gly Phe Gly His Asn Tyr Arg Pro His Arg Thr Val Ser Thr
805 810 815

Ser Ser Thr Ser Gly Asn Asp Phe Glu Glu Thr Lys Ala His Ile Arg
820 825 830

Phe Ser Glu Ser Ala Glu Pro Leu Gly Asn Gly Glu Gln His Phe Lys
835 840 845

Asn Gly Glu Leu Lys Leu Glu Glu Ala Ser Arg Gln Pro Cys Gly Gln
850 855 860

Gln Leu Ser Gly Gly Ala Ser Asp Ser Gly Arg Gly Pro Gln Arg Pro
865 870 875 880

Asp Ala Arg Leu Leu Arg Ser Gln Ser Thr Phe Gln Leu Ser Ser Glu
885 890 895

Pro Glu Arg Glu Pro Glu Trp Arg Asp Arg Pro Gly Ser Pro Glu Ser
900 905 910

Pro Leu Leu Asp Ala Pro Phe Ser Arg Ala Tyr Arg Asn Ser Ile Lys
915 920 925

Asp Ala Gln Ser Arg Val Leu Gly Ala Thr Ser Phe Arg Arg Arg Asp
930 935 940

Leu Glu Leu Gly Ala Pro Val Ala Ser Arg Ser Trp Arg Pro Arg Pro
945 950 955 960

Ser Ser Ala His Val Gly Leu Arg Ser Pro Glu Ala Ser Ala Ser Ala
965 970 975

Ser Pro His Thr Pro Arg Glu Arg His Ser Val Thr Pro Ala Glu Gly
980 985 990

Asp Leu Ala Arg Pro Val Pro Pro Ala Ala Arg Arg Gly Ala Arg Arg
995 1000 1005

Arg Leu Thr Pro Glu Gln Lys Lys Arg Ser Tyr Ser Glu Pro Glu
1010 1015 1020

Lys Met Asn Glu Val Gly Ile Val Glu Glu Ala Glu Pro Ala Pro
1025 1030 1035

Leu Gly Pro Gln Arg Asn Gly Met Arg Phe Pro Glu Ser Ser Val
1040 1045 1050

Ala Asp Arg Arg Arg Leu Phe Glu Arg Asp Gly Lys Ala Cys Ser
1055 1060 1065

Thr Leu Ser Leu Ser Gly Pro Glu Leu Lys Gln Phe Gln Gln Ser
1070 1075 1080

Ala Leu Ala Asp Tyr Ile Gln Arg Lys Thr Gly Lys Arg Pro Thr
1085 1090 1095

Ser Ala Ala Gly Cys Ser Leu Gln Glu Pro Gly Pro Leu Arg Glu
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Arg Ala Gln Ser Ala Tyr Leu Gln Pro Gly Pro Ala Ala Leu Glu
1115 1120 1125

Gly Ser Gly Leu Ala Ser Ala Ser Ser Leu Ser Ser Leu Arg Glu
1130 1135 1140

Pro Ser Leu Gln Pro Arg Arg Glu Ala Thr Leu Leu Pro Ala Thr
1145 1150 1155

Val Ala Glu Thr Gln Gln Ala Pro Arg Asp Arg Ser Ser Ser Phe
1160 1165 1170

Ala Gly Gly Arg Arg Leu Gly Glu Arg Arg Arg Gly Asp Leu Leu
1175 1180 1185

Ser Gly Ala Asn Gly Gly Thr Arg Gly Thr Gln Arg Gly Asp Glu
1190 1195 1200

Thr Pro Arg Glu Pro Ser Ser Trp Gly Ala Arg Ala Gly Lys Ser
1205 1210 1215

Met Ser Ala Glu Asp Leu Leu Glu Arg Ser Asp Val Leu Ala Gly
1220 1225 1230

Pro Val His Val Arg Ser Arg Ser Ser Pro Ala Thr Ala Asp Lys
1235 1240 1245

Arg Gln Asp Val Leu Leu Gly Gln Asp Ser Gly Phe Gly Leu Val
1250 1255 1260

Lys Asp Pro Cys Tyr Leu Ala Gly Pro Gly Ser Arg Ser Leu Ser
1265 1270 1275

Cys Ser Glu Arg Gly Gln Glu Glu Met Leu Leu Leu Phe His His
1280 1285 1290

Leu Thr Pro Arg Trp Gly Gly Ser Gly Cys Lys Ala Ile Gly Asp
1295 1300 1305

Ser Ser Val Pro Ser Glu Cys Pro Gly Thr Leu Asp His Gln Arg
1310 1315 1320

Gln Ala Ser Arg Thr Pro Cys Pro Arg Pro Pro Leu Ala Gly Thr
1325 1330 1335

Gln Gly Leu Val Thr Asp Thr Arg Ala Ala Pro Leu Thr Pro Ile
1340 1345 1350

Gly Thr Pro Leu Pro Ser Ala Ile Pro Ser Gly Tyr Cys Ser Gln
1355 1360 1365

Asp Gly Gln Thr Gly Arg Gln Pro Leu Pro Pro Tyr Thr Pro Ala
1370 1375 1380

Met Met His Arg Ser Asn Gly His Thr Leu Thr Gln Pro Pro Gly
1385 1390 1395

Pro Arg Gly Cys Glu Gly Asp Gly Pro Glu His Gly Val Glu Glu
1400 1405 1410

Gly Thr Arg Lys Arg Val Ser Leu Pro Gln Trp Pro Pro Pro Ser
1415 1420 1425

Arg Ala Lys Trp Ala His Ala Ala Arg Glu Asp Ser Leu Pro Glu
1430 1435 1440

Glu Ser Ser Ala Pro Asp Phe Ala Asn Leu Lys His Tyr Gln Lys
1445 1450 1455

Gln Gln Ser Leu Pro Ser Leu Cys Ser Thr Ser Asp Pro Asp Thr
1460 1465 1470

Pro Leu Gly Ala Pro Ser Thr Pro Gly Arg Ile Ser Leu Arg Ile
1475 1480 1485

Ser Glu Ser Val Leu Arg Asp Ser Pro Pro Pro His Glu Asp Tyr
1490 1495 1500

Glu Asp Glu Val Phe Val Arg Asp Pro His Pro Lys Ala Thr Ser
1505 1510 1515

Ser Pro Thr Phe Glu Pro Leu Pro Pro Pro Pro Pro Pro Pro Pro
1520 1525 1530

Ser Gln Glu Thr Pro Val Tyr Ser Met Asp Asp Phe Pro Pro Pro
1535 1540 1545

Pro Pro His Thr Val Cys Glu Ala Gln Leu Asp Ser Glu Asp Pro
1550 1555 1560

Glu Gly Pro Arg Pro Ser Phe Asn Lys Leu Ser Lys Val Thr Ile
1565 1570 1575

Ala Arg Glu Arg His Met Pro Gly Ala Ala His Val Val Gly Ser
1580 1585 1590

Gln Thr Leu Ala Ser Arg Leu Gln Thr Ser Ile Lys Gly Ser Glu
1595 1600 1605

Ala Glu Ser Thr Pro Pro Ser Phe Met Ser Val His Ala Gln Leu
1610 1615 1620

Ala Gly Ser Leu Gly Gly Gln Pro Ala Pro Ile Gln Thr Gln Ser
1625 1630 1635

Leu Ser His Asp Pro Val Ser Gly Thr Gln Gly Leu Glu Lys Lys
1640 1645 1650

Val Ser Pro Asp Pro Gln Lys Ser Ser Glu Asp Ile Arg Thr Glu
1655 1660 1665

Ala Leu Ala Lys Glu Ile Val His Gln Asp Lys Ser Leu Ala Asp
1670 1675 1680

Ile Leu Asp Pro Asp Ser Arg Leu Lys Thr Thr Met Asp Leu Met
1685 1690 1695

Glu Gly Leu Phe Pro Arg Asp Val Asn Leu Leu Lys Glu Asn Ser
1700 1705 1710

Val Lys Arg Lys Ala Ile Gln Arg Thr Val Ser Ser Ser Gly Cys
1715 1720 1725

Glu Gly Lys Arg Asn Glu Asp Lys Glu Ala Val Ser Met Leu Val
1730 1735 1740

Asn Cys Pro Ala Tyr Tyr Ser Val Ser Ala Pro Lys Ala Glu Leu
1745 1750 1755

Leu Asn Lys Ile Lys Glu Met Pro Ala Glu Val Asn Glu Glu Glu
1760 1765 1770

Glu Gln Ala Asp Val Asn Glu Lys Lys Ala Glu Leu Ile Gly Ser
1775 1780 1785

Leu Thr His Lys Leu Glu Thr Leu Gln Glu Ala Lys Gly Ser Leu
1790 1795 1800

Leu Thr Asp Ile Lys Leu Asn Asn Ala Leu Gly Glu Glu Val Glu
1805 1810 1815

Ala Leu Ile Ser Glu Leu Cys Lys Pro Asn Glu Phe Asp Lys Tyr
1820 1825 1830

Arg Met Phe Ile Gly Asp Leu Asp Lys Val Val Asn Leu Leu Leu
1835 1840 1845

Ser Leu Ser Gly Arg Leu Ala Arg Val Glu Asn Val Leu Ser Gly
1850 1855 1860

Leu Gly Glu Asp Ala Ser Asn Glu Glu Arg Ser Ser Leu Tyr Glu
1865 1870 1875

Lys Arg Lys Ile Leu Ala Gly Gln His Glu Asp Ala Arg Glu Leu
1880 1885 1890

Lys Glu Asn Leu Asp Arg Arg Glu Arg Val Val Leu Gly Ile Leu
1895 1900 1905

Ala Asn Tyr Leu Ser Glu Glu Gln Leu Gln Asp Tyr Gln His Phe
1910 1915 1920

Val Lys Met Lys Ser Thr Leu Leu Ile Glu Gln Arg Lys Leu Asp
1925 1930 1935

Asp Lys Ile Lys Leu Gly Gln Glu Gln Val Lys Cys Leu Leu Glu
1940 1945 1950

Ser Leu Pro Ser Asp Phe Ile Pro Lys Ala Gly Ala Leu Ala Leu
1955 1960 1965

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Pro Pro Asn Leu Thr Ser Glu Pro Ile Pro Ala Gly Gly Cys Thr
    1970                1975                1980

Phe Ser Gly Ile Phe Pro Thr Leu Thr Ser Pro Leu
    1985                1990                1995


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cagcgctacc tggcggaact ggatttctct cccgcctgcc ggcctgcctg ccacagccgg     180

actccgccac tccggtagcc tc atg gct gca acc tgt gag att agc aac att      232
                         Met Ala Ala Thr Cys Glu Ile Ser Asn Ile
                         1               5                   10

ttt agc aac tac ttc agt gcg atg tac agc tcg gag gac tcc acc ctg      280
Phe Ser Asn Tyr Phe Ser Ala Met Tyr Ser Ser Glu Asp Ser Thr Leu
                15                  20                  25

gcc tct gtt ccc cct gct gcc acc ttt ggg gcc gat gac ttg gta ctg      328
Ala Ser Val Pro Pro Ala Ala Thr Phe Gly Ala Asp Asp Leu Val Leu
            30                  35                  40

acc ctg agc aac ccc cag atg tca ttg gag ggt aca gag aag gcc agc      376
Thr Leu Ser Asn Pro Gln Met Ser Leu Glu Gly Thr Glu Lys Ala Ser
        45                  50                  55

tgg ttg ggg gaa cag ccc cag ttc tgg tcg aag acg cag gtt ctg gac      424
Trp Leu Gly Glu Gln Pro Gln Phe Trp Ser Lys Thr Gln Val Leu Asp
    60                  65                  70

tgg atc agc tac caa gtg gag aag aac aag tac gac gca agc gcc att      472
Trp Ile Ser Tyr Gln Val Glu Lys Asn Lys Tyr Asp Ala Ser Ala Ile
75                  80                  85                  90

gac ttc tca cga tgt gac atg gat ggc gcc acc ctc tgc aat tgt gcc      520
Asp Phe Ser Arg Cys Asp Met Asp Gly Ala Thr Leu Cys Asn Cys Ala
                95                  100                 105

ctt gag gag ctg cgt ctg gtc ttt ggg cct ctg ggg gac caa ctc cat      568
Leu Glu Glu Leu Arg Leu Val Phe Gly Pro Leu Gly Asp Gln Leu His
            110                 115                 120
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gcc cag ctg cga gac ctc act tcc agc tct tct gat gag ctc agt tgg       616
Ala Gln Leu Arg Asp Leu Thr Ser Ser Ser Ser Asp Glu Leu Ser Trp
        125                 130                 135

atc att gag ctg ctg gag aag gat ggc atg gcc ttc cag gag gcc cta       664
Ile Ile Glu Leu Leu Glu Lys Asp Gly Met Ala Phe Gln Glu Ala Leu
    140                 145                 150

gac cca ggg ccc ttt gac cag ggc agc ccc ttt gcc cag gag ctg ctg       712
Asp Pro Gly Pro Phe Asp Gln Gly Ser Pro Phe Ala Gln Glu Leu Leu
155                 160                 165                 170

gac gac ggt cag caa gcc agc ccc tac cac ccc ggc agc tgt ggc gca       760
Asp Asp Gly Gln Gln Ala Ser Pro Tyr His Pro Gly Ser Cys Gly Ala
                175                 180                 185

gga gcc ccc tcc ccc ggc agc tct gac gtc tcc acc gca ggg act ggt       808
Gly Ala Pro Ser Pro Gly Ser Ser Asp Val Ser Thr Ala Gly Thr Gly
            190                 195                 200

gct tct cgg agc tcc cac tcc tca gac tcc ggt gga agt gac gtg gac       856
Ala Ser Arg Ser Ser His Ser Ser Asp Ser Gly Gly Ser Asp Val Asp
        205                 210                 215

ctg gat ccc act gat ggc aag ctc ttc ccc agc gat ggt ttt cgt gac       904
Leu Asp Pro Thr Asp Gly Lys Leu Phe Pro Ser Asp Gly Phe Arg Asp
    220                 225                 230

tgc aag aag ggg gat ccc aag cac ggg aag cgg aaa cga ggc cgg ccc       952
Cys Lys Lys Gly Asp Pro Lys His Gly Lys Arg Lys Arg Gly Arg Pro
235                 240                 245                 250

cga aag ctg agc aaa gag tac tgg gac tgt ctc gag ggc aag aag agc      1000
Arg Lys Leu Ser Lys Glu Tyr Trp Asp Cys Leu Glu Gly Lys Lys Ser
                255                 260                 265

aag cac gcg ccc aga ggc acc cac ctg tgg gag ttc atc cgg gac atc      1048
Lys His Ala Pro Arg Gly Thr His Leu Trp Glu Phe Ile Arg Asp Ile
            270                 275                 280

ctc atc cac ccg gag ctc aac gag ggc ctc atg aag tgg gag aat cgg      1096
Leu Ile His Pro Glu Leu Asn Glu Gly Leu Met Lys Trp Glu Asn Arg
        285                 290                 295

cat gaa ggc gtc ttc aag ttc ctg cgc tcc gag gct gtg gcc caa cta      1144
His Glu Gly Val Phe Lys Phe Leu Arg Ser Glu Ala Val Ala Gln Leu
    300                 305                 310

tgg ggc caa aag aaa aag aac agc aac atg acc tac gag aag ctg agc      1192
Trp Gly Gln Lys Lys Lys Asn Ser Asn Met Thr Tyr Glu Lys Leu Ser
315                 320                 325                 330

cgg gcc atg agg tac tac tac aaa cgg gag atc ctg gaa cgg gtg gat      1240
Arg Ala Met Arg Tyr Tyr Tyr Lys Arg Glu Ile Leu Glu Arg Val Asp
                335                 340                 345

ggc cgg cga ctc gtc tac aag ttt ggc aaa aac tca agc ggc tgg aag      1288
Gly Arg Arg Leu Val Tyr Lys Phe Gly Lys Asn Ser Ser Gly Trp Lys
            350                 355                 360

gag gaa gag gtt ctc cag agt cgg aac tgagggttgg aactataccc           1335
Glu Glu Glu Val Leu Gln Ser Arg Asn
        365                 370

gggaccaaac tcacggacca ctcgaggcct gcaaaccttc ctgggaggac aggcaggcca   1395

gatggcccct ccactgggga atgctcccag ctgtgctgtg gagagaagct gatgttttgg   1455
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tgtattgtca gccatcgtcc ttggactcgg agactatggc ctcgcctccc caccctcctc 1515

ttggaattac aagccctggg gtttgaagct gactttatag ctgcaagtgt atctcctttt 1575

atctggtgcc tcctcaaacc cagtctcaga cactaaatgc agacaacacc ttcctcctgc 1635

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ttttgcattc cagccaagtg tgctgtaaac tgtatatctg taatatgaat cccagctttt 2475

gagtctgaca aaatcagagt taggatcttg taaaggaaaa aaaaaaaaaa aaaa 2529

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20 25 30

Ala Thr Phe Gly Ala Asp Asp Leu Val Leu Thr Leu Ser Asn Pro Gln
35 40 45

Met Ser Leu Glu Gly Thr Glu Lys Ala Ser Trp Leu Gly Glu Gln Pro
50 55 60

Gln Phe Trp Ser Lys Thr Gln Val Leu Asp Trp Ile Ser Tyr Gln Val
65 70 75 80

Glu Lys Asn Lys Tyr Asp Ala Ser Ala Ile Asp Phe Ser Arg Cys Asp
85 90 95

Met Asp Gly Ala Thr Leu Cys Asn Cys Ala Leu Glu Glu Leu Arg Leu
100 105 110

Val Phe Gly Pro Leu Gly Asp Gln Leu His Ala Gln Leu Arg Asp Leu
115 120 125

Thr Ser Ser Ser Ser Asp Glu Leu Ser Trp Ile Ile Glu Leu Leu Glu
130 135 140

Lys Asp Gly Met Ala Phe Gln Glu Ala Leu Asp Pro Gly Pro Phe Asp
145 150 155 160

Gln Gly Ser Pro Phe Ala Gln Glu Leu Leu Asp Asp Gly Gln Gln Ala
165 170 175

Ser Pro Tyr His Pro Gly Ser Cys Gly Ala Gly Ala Pro Ser Pro Gly
180 185 190

Ser Ser Asp Val Ser Thr Ala Gly Thr Gly Ala Ser Arg Ser Ser His
195 200 205

Ser Ser Asp Ser Gly Gly Ser Asp Val Asp Leu Asp Pro Thr Asp Gly
210 215 220

Lys Leu Phe Pro Ser Asp Gly Phe Arg Asp Cys Lys Lys Gly Asp Pro
225 230 235 240

Lys His Gly Lys Arg Lys Arg Gly Arg Pro Arg Lys Leu Ser Lys Glu
245 250 255

Tyr Trp Asp Cys Leu Glu Gly Lys Lys Ser Lys His Ala Pro Arg Gly
260 265 270

Thr His Leu Trp Glu Phe Ile Arg Asp Ile Leu Ile His Pro Glu Leu
275 280 285

Asn Glu Gly Leu Met Lys Trp Glu Asn Arg His Glu Gly Val Phe Lys
290 295 300

Phe Leu Arg Ser Glu Ala Val Ala Gln Leu Trp Gly Gln Lys Lys Lys
305 310 315 320

Asn Ser Asn Met Thr Tyr Glu Lys Leu Ser Arg Ala Met Arg Tyr Tyr
325 330 335

Tyr Lys Arg Glu Ile Leu Glu Arg Val Asp Gly Arg Arg Leu Val Tyr

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Lys Phe Gly Lys Asn Ser Ser Gly Trp Lys Glu Glu Glu Val Leu Gln
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Ser Arg Asn
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<212> DNA

<213> NM_019027 FLJ20273

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ataagatgga acccatccac ataaggattt gcctcaaagg gcactgcaaa aattgaacag     120

aggaatccca aggaagctgc ctgaatttgc ctgtatactc tcgttctgcg acttataaag     180

gaccagacaa atcaaattag tggttttggt ttccgccagc tgtggatgcc tttgacatt      239

atg acc gca gag gat tcc acc gca gcc atg agc agt gac tcg gcc gcc       287
Met Thr Ala Glu Asp Ser Thr Ala Ala Met Ser Ser Asp Ser Ala Ala
1               5                   10                  15

ggg tcc tcg gcc aag gtg ccc gag ggc gtg gcg ggc gcg ccc aac gag       335
Gly Ser Ser Ala Lys Val Pro Glu Gly Val Ala Gly Ala Pro Asn Glu
            20                  25                  30

gca gca ctg ctg gcg ctg atg gag cgc acg ggc tac agc atg gtg caa       383
Ala Ala Leu Leu Ala Leu Met Glu Arg Thr Gly Tyr Ser Met Val Gln
        35                  40                  45

gag aac ggg cag cgc aag tac ggc ggc cca ccg ccc ggc tgg gag ggc       431
Glu Asn Gly Gln Arg Lys Tyr Gly Gly Pro Pro Pro Gly Trp Glu Gly
    50                  55                  60

ccg cac ccg cag cgt ggc tgc gag gtc ttc gtg ggc aag atc ccg cgc       479
Pro His Pro Gln Arg Gly Cys Glu Val Phe Val Gly Lys Ile Pro Arg
65                  70                  75                  80

gac gtg tac gag gac gag ctg gtg ccc gtg ttc gag gcc gtg ggc cgc       527
Asp Val Tyr Glu Asp Glu Leu Val Pro Val Phe Glu Ala Val Gly Arg
                85                  90                  95

acc tac gag ctg cgc ctc atg atg gac ttt gac ggc aag aac cgc ggc       575
Thr Tyr Glu Leu Arg Leu Met Met Asp Phe Asp Gly Lys Asn Arg Gly
            100                 105                 110
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tac gcc ttc gtc atg tac tgc cac aag cac gag gcc aag cgc gca gtg      623
Tyr Ala Phe Val Met Tyr Cys His Lys His Glu Ala Lys Arg Ala Val
        115                 120                 125

cgt gag ctc aac aac tac gag atc cgc ccg ggc cgc ctg ctc ggc gtg      671
Arg Glu Leu Asn Asn Tyr Glu Ile Arg Pro Gly Arg Leu Leu Gly Val
    130                 135                 140

tgc tgc agc gtg gac aac tgc cgc ctc ttc atc ggc ggg atc ccc aag      719
Cys Cys Ser Val Asp Asn Cys Arg Leu Phe Ile Gly Gly Ile Pro Lys
145                 150                 155                 160

atg aag aag cgc gag gaa atc ctg gag gag att gcc aag gtc acc gag      767
Met Lys Lys Arg Glu Glu Ile Leu Glu Glu Ile Ala Lys Val Thr Glu
                165                 170                 175

ggc gtg ctg gac gtg atc gtc tac gcc agc gcg gcc gac aag atg aag      815
Gly Val Leu Asp Val Ile Val Tyr Ala Ser Ala Ala Asp Lys Met Lys
            180                 185                 190

aac cgc ggc ttc gcc ttc gtg gag tac gag agc cac cgc gcg gct gcc      863
Asn Arg Gly Phe Ala Phe Val Glu Tyr Glu Ser His Arg Ala Ala Ala
        195                 200                 205

atg gct cgc cgc aag ctc atg cct ggc cgc atc cag ctg tgg ggc cac      911
Met Ala Arg Arg Lys Leu Met Pro Gly Arg Ile Gln Leu Trp Gly His
    210                 215                 220

cag atc gcc gtg gac tgg gcc gag cct gag atc gac gtg gac gag gac      959
Gln Ile Ala Val Asp Trp Ala Glu Pro Glu Ile Asp Val Asp Glu Asp
225                 230                 235                 240

gtg atg gag acc gtg aag atc ctc tac gtg cgc aac ctc atg atc gag     1007
Val Met Glu Thr Val Lys Ile Leu Tyr Val Arg Asn Leu Met Ile Glu
                245                 250                 255

acc acc gag gac acc atc aag aag agc ttc ggc cag ttc aac ccc ggc     1055
Thr Thr Glu Asp Thr Ile Lys Lys Ser Phe Gly Gln Phe Asn Pro Gly
            260                 265                 270

tgc gtg gag cgc gtc aag aag atc cgc gac tac gcc ttc gtg cac ttc     1103
Cys Val Glu Arg Val Lys Lys Ile Arg Asp Tyr Ala Phe Val His Phe
        275                 280                 285

acc agc cgc gag gat gcc gtg cat gcc atg aac aac ctc aac ggc act     1151
Thr Ser Arg Glu Asp Ala Val His Ala Met Asn Asn Leu Asn Gly Thr
    290                 295                 300

gag ctg gag ggc tcg tgc ctg gag gtc acg ctg gcc aag ccc gtg gac     1199
Glu Leu Glu Gly Ser Cys Leu Glu Val Thr Leu Ala Lys Pro Val Asp
305                 310                 315                 320

aag gag cag tac tcg cgc tac cag aag gca gcc agg ggc ggc ggc gcg     1247
Lys Glu Gln Tyr Ser Arg Tyr Gln Lys Ala Ala Arg Gly Gly Gly Ala
                325                 330                 335

gct gag gca gcg cag cag ccc agc tac gtg tac tcc tgc gac ccc tac     1295
Ala Glu Ala Ala Gln Gln Pro Ser Tyr Val Tyr Ser Cys Asp Pro Tyr
            340                 345                 350

aca ctg gcc tac tac ggc tac ccc tac aac gcg ctc att ggg ccc aac     1343
Thr Leu Ala Tyr Tyr Gly Tyr Pro Tyr Asn Ala Leu Ile Gly Pro Asn
        355                 360                 365

agg gac tac ttt gtg aaa gta gcc atc cct gcc att ggg gct cag tat     1391
Arg Asp Tyr Phe Val Lys Val Ala Ile Pro Ala Ile Gly Ala Gln Tyr
    370                 375                 380
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tcc atg ttt cca gca gct cca gcc cct aaa atg att gaa gat ggc aaa      1439
Ser Met Phe Pro Ala Ala Pro Ala Pro Lys Met Ile Glu Asp Gly Lys
385                 390                 395                 400

atc cac aca gtg gag cac atg atc agc ccc att gct gtg cag cca gac      1487
Ile His Thr Val Glu His Met Ile Ser Pro Ile Ala Val Gln Pro Asp
                405                 410                 415

cca gcc agt gct gct gcc gcc gca gcc gcg gcc gca gcc gcc gca gcc      1535
Pro Ala Ser Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala
            420                 425                 430

gct gtc att ccc act gtg tcg acg cca cca cct ttc cag ggc cgc cca      1583
Ala Val Ile Pro Thr Val Ser Thr Pro Pro Pro Phe Gln Gly Arg Pro
        435                 440                 445

ata act cca gta tac acg gtg gct cca aac gtt cag aga att cct act      1631
Ile Thr Pro Val Tyr Thr Val Ala Pro Asn Val Gln Arg Ile Pro Thr
    450                 455                 460

gcc ggg atc tac ggg gcc agt tac gtg cca ttt gct gct cca gct aca      1679
Ala Gly Ile Tyr Gly Ala Ser Tyr Val Pro Phe Ala Ala Pro Ala Thr
465                 470                 475                 480

gcc acg atc gcc aca cta cag aag aac gcg gca gcc gcg gcc gcc gtg      1727
Ala Thr Ile Ala Thr Leu Gln Lys Asn Ala Ala Ala Ala Ala Ala Val
                485                 490                 495

tat gga gga tac gca ggc tac ata cct cag gcc ttc cct gct gct gcc      1775
Tyr Gly Gly Tyr Ala Gly Tyr Ile Pro Gln Ala Phe Pro Ala Ala Ala
            500                 505                 510

att cag gtc ccc atc ccc gac gtc tac cag aca tac tgaggctggt           1821
Ile Gln Val Pro Ile Pro Asp Val Tyr Gln Thr Tyr
        515                 520

gaccagcacg aagacagacc acacaaacac cactgaagga acgcttgact atttatgaag    1881

aaggaacatg ttggattcac acatgcaacc tgaaagtgaa gaatgttagc agatttattt    1941

ctgaattatt ttatatacat gaagttttca ctagtttttt aagactattt tcaacttagc    2001

atgcctacgt tcatacattt ccaaaagact tgcaatggtt cgtgccttca ttccatcttt    2061

taaaaatttg tatgctgtac tacatttgta tagaggtttt tgttgttgtt tttttaagga    2121

tatattttca gtatgaaggt tattttctta acttctgcac tccagagatt tctattttgt    2181

agtaccttca ataatatatc aactatatat taaaaaagca cacttgagga gctagggaac    2241

tattttgaaa aatatataca atatttaaag atacaaacag tagtgcttaa aaatactaca    2301

taaagcatta ttttaaaggt tatactggaa agtgcaattt taaaatgagt aaaacctctg    2361

tatttctgct ggcattaagg gttgatggtg ttaccatgta tcatcatggc ggtactattt    2421

tttaaaagaa attaaacact ggatctctcc ttaagccaac attgaaaaga cttgccgcac    2481

ttctgagtcc aaacactgga aagctctcct tgccaccgtt agccggggct cattctccat    2541

gtgccttagc cttaaacatg cccccactcc cacatctctc accctgtccc ctcctcccca    2601

gattcccaat cccaccgcaa tgtttggcaa gcctaggact gataagtagc tctgatagag    2661

gagctggtgg cttttatact tcttcctggg tttttgttgg ggtttgttgt ttcgttgttt    2721

tttgtttttt ttttgtttgg ttggggaagt attgtcttct acgtgtgcta ttttcagtag    2781
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cagagtaagc acaaggtttt aatcgagttg cataagacac ctttgcatag ctatttaatt 2841
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gatttttgtt gatggctgaa ttcttgtgga ttcataagag gatcatgccc ttagcaagta 3561
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gagatgagtt tttatgtgta agcaatattt atttaactat tctataaaat tattgagtgc 3681
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gaatgagtga ctcgaccaaa tgtaattcgg atcagatcct catcccctga ctgtgtgaaa 3861
aaagtactct ccttctagtg aaggattgtc acagagtttc actggatgaa actatgaccc 3921
agtattctta ctgtatttta catgtgcctg taaattattt tgccgaaata agaagaagaa 3981
gaggaagaaa gaacagtaga aaaaaaaaat aaaaaaaaa 4020

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<212> PRT

<213> NM_019027 FLJ20273

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Met Thr Ala Glu Asp Ser Thr Ala Ala Met Ser Ser Asp Ser Ala Ala
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Gly Ser Ser Ala Lys Val Pro Glu Gly Val Ala Gly Ala Pro Asn Glu
            20   25   30

Ala Ala Leu Leu Ala Leu Met Glu Arg Thr Gly Tyr Ser Met Val Gln
        35   40   45

Glu Asn Gly Gln Arg Lys Tyr Gly Gly Pro Pro Pro Gly Trp Glu Gly

```
50                  55                  60

Pro His Pro Gln Arg Gly Cys Glu Val Phe Val Gly Lys Ile Pro Arg
65                  70                  75                  80

Asp Val Tyr Glu Asp Glu Leu Val Pro Val Phe Glu Ala Val Gly Arg
                85                  90                  95

Thr Tyr Glu Leu Arg Leu Met Met Asp Phe Asp Gly Lys Asn Arg Gly
            100                 105                 110

Tyr Ala Phe Val Met Tyr Cys His Lys His Glu Ala Lys Arg Ala Val
        115                 120                 125

Arg Glu Leu Asn Asn Tyr Glu Ile Arg Pro Gly Arg Leu Leu Gly Val
    130                 135                 140

Cys Cys Ser Val Asp Asn Cys Arg Leu Phe Ile Gly Gly Ile Pro Lys
145                 150                 155                 160

Met Lys Lys Arg Glu Glu Ile Leu Glu Glu Ile Ala Lys Val Thr Glu
                165                 170                 175

Gly Val Leu Asp Val Ile Val Tyr Ala Ser Ala Ala Asp Lys Met Lys
            180                 185                 190

Asn Arg Gly Phe Ala Phe Val Glu Tyr Glu Ser His Arg Ala Ala Ala
        195                 200                 205

Met Ala Arg Arg Lys Leu Met Pro Gly Arg Ile Gln Leu Trp Gly His
    210                 215                 220

Gln Ile Ala Val Asp Trp Ala Glu Pro Glu Ile Asp Val Asp Glu Asp
225                 230                 235                 240

Val Met Glu Thr Val Lys Ile Leu Tyr Val Arg Asn Leu Met Ile Glu
                245                 250                 255

Thr Thr Glu Asp Thr Ile Lys Lys Ser Phe Gly Gln Phe Asn Pro Gly
            260                 265                 270

Cys Val Glu Arg Val Lys Lys Ile Arg Asp Tyr Ala Phe Val His Phe
        275                 280                 285

Thr Ser Arg Glu Asp Ala Val His Ala Met Asn Asn Leu Asn Gly Thr
    290                 295                 300

Glu Leu Glu Gly Ser Cys Leu Glu Val Thr Leu Ala Lys Pro Val Asp
305                 310                 315                 320

Lys Glu Gln Tyr Ser Arg Tyr Gln Lys Ala Ala Arg Gly Gly Gly Ala
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325 330 335

Ala Glu Ala Ala Gln Gln Pro Ser Tyr Val Tyr Ser Cys Asp Pro Tyr
340 345 350

Thr Leu Ala Tyr Tyr Gly Tyr Pro Tyr Asn Ala Leu Ile Gly Pro Asn
355 360 365

Arg Asp Tyr Phe Val Lys Val Ala Ile Pro Ala Ile Gly Ala Gln Tyr
370 375 380

Ser Met Phe Pro Ala Ala Pro Ala Pro Lys Met Ile Glu Asp Gly Lys
385 390 395 400

Ile His Thr Val Glu His Met Ile Ser Pro Ile Ala Val Gln Pro Asp
405 410 415

Pro Ala Ser Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala
420 425 430

Ala Val Ile Pro Thr Val Ser Thr Pro Pro Pro Phe Gln Gly Arg Pro
435 440 445

Ile Thr Pro Val Tyr Thr Val Ala Pro Asn Val Gln Arg Ile Pro Thr
450 455 460

Ala Gly Ile Tyr Gly Ala Ser Tyr Val Pro Phe Ala Ala Pro Ala Thr
465 470 475 480

Ala Thr Ile Ala Thr Leu Gln Lys Asn Ala Ala Ala Ala Ala Ala Val
485 490 495

Tyr Gly Gly Tyr Ala Gly Tyr Ile Pro Gln Ala Phe Pro Ala Ala Ala
500 505 510

Ile Gln Val Pro Ile Pro Asp Val Tyr Gln Thr Tyr
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tgagggcctg cagccggccg gccagggcag cggcaggcgc ggcccggacc tacgggagga     120

agccccgagc cctcggcggg ctgcgagcga ctccccggcg atg cct cac aac tcc       175
                                            Met Pro His Asn Ser
                                            1               5

atc aga tct ggc cat gga ggg ctg aac cag ctg gga ggg gcc ttt gtg       223
Ile Arg Ser Gly His Gly Gly Leu Asn Gln Leu Gly Gly Ala Phe Val
            10                  15                  20

aat ggc aga cct ctg ccg gaa gtg gtc cgc cag cgc atc gta gac ctg       271
Asn Gly Arg Pro Leu Pro Glu Val Val Arg Gln Arg Ile Val Asp Leu
        25                  30                  35

gcc cac cag ggt gta agg ccc tgc gac atc tct cgc cag ctc cgc gtc       319
Ala His Gln Gly Val Arg Pro Cys Asp Ile Ser Arg Gln Leu Arg Val
    40                  45                  50

agc cat ggc tgc gtc agc aag atc ctt ggc agg tac tac gag act ggc       367
Ser His Gly Cys Val Ser Lys Ile Leu Gly Arg Tyr Tyr Glu Thr Gly
    55                  60                  65

agc atc cgg cct gga gtg ata ggg ggc tcc aag ccc aag gtg gcc acc       415
Ser Ile Arg Pro Gly Val Ile Gly Gly Ser Lys Pro Lys Val Ala Thr
70                  75                  80                  85

ccc aag gtg gtg gag aag att ggg gac tac aaa cgc cag aac cct acc       463
Pro Lys Val Val Glu Lys Ile Gly Asp Tyr Lys Arg Gln Asn Pro Thr
            90                  95                  100

atg ttt gcc tgg gag atc cga gac cgg ctc ctg gct gag ggc gtc tgt       511
Met Phe Ala Trp Glu Ile Arg Asp Arg Leu Leu Ala Glu Gly Val Cys
        105                 110                 115

gac aat gac act gtg ccc agt gtc agc tcc att aat aga atc atc cgg       559
Asp Asn Asp Thr Val Pro Ser Val Ser Ser Ile Asn Arg Ile Ile Arg
    120                 125                 130

acc aaa gtg cag caa cca ttc aac ctc cct atg gac agc tgc gtg gcc       607
Thr Lys Val Gln Gln Pro Phe Asn Leu Pro Met Asp Ser Cys Val Ala
    135                 140                 145

acc aag tcc ctg agt ccc gga cac acg ctg atc ccc agc tca gct gta       655
Thr Lys Ser Leu Ser Pro Gly His Thr Leu Ile Pro Ser Ser Ala Val
150                 155                 160                 165

act ccc ccg gag tca ccc cag tcg gat tcc ctg ggc tcc acc tac tcc       703
Thr Pro Pro Glu Ser Pro Gln Ser Asp Ser Leu Gly Ser Thr Tyr Ser
            170                 175                 180

atc aat ggg ctc ctg ggc atc gct cag cct ggc agc gac aag agg aaa       751
Ile Asn Gly Leu Leu Gly Ile Ala Gln Pro Gly Ser Asp Lys Arg Lys
        185                 190                 195

atg gat gac agt gat cag gat agc tgc cga cta agc att gac tca cag       799
Met Asp Asp Ser Asp Gln Asp Ser Cys Arg Leu Ser Ile Asp Ser Gln
    200                 205                 210

agc agc agc agc gga ccc cga aag cac ctt cgc acg gat gcc ttc agc       847
Ser Ser Ser Ser Gly Pro Arg Lys His Leu Arg Thr Asp Ala Phe Ser
    215                 220                 225
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cag cac cac ctc gag ccg ctc gag tgc cca ttt gag cgg cag cac tac        895
Gln His His Leu Glu Pro Leu Glu Cys Pro Phe Glu Arg Gln His Tyr
230                 235                 240                 245

cca gag gcc tat gcc tcc ccc agc cac acc aaa ggc gag cag ggc ctc        943
Pro Glu Ala Tyr Ala Ser Pro Ser His Thr Lys Gly Glu Gln Gly Leu
                250                 255                 260

tac ccg ctg ccc ttg ctc aac agc acc ctg gac gac ggg aag gcc acc        991
Tyr Pro Leu Pro Leu Leu Asn Ser Thr Leu Asp Asp Gly Lys Ala Thr
            265                 270                 275

ctg acc cct tcc aac acg cca ctg ggg cgc aac ctc tcg act cac cag       1039
Leu Thr Pro Ser Asn Thr Pro Leu Gly Arg Asn Leu Ser Thr His Gln
        280                 285                 290

acc tac ccc gtg gtg gca gct ccg ccc ttt tgg atc tgc agc aag tcg       1087
Thr Tyr Pro Val Val Ala Ala Pro Pro Phe Trp Ile Cys Ser Lys Ser
    295                 300                 305

gct ccg ggg tcc cgc cct tca atg cct ttc ccc atg ctg cct ccg tgt       1135
Ala Pro Gly Ser Arg Pro Ser Met Pro Phe Pro Met Leu Pro Pro Cys
310                 315                 320                 325

acg ggc agt tca cgg gcc agg ccc tcc tct cag ggc gag aga tgg tgg       1183
Thr Gly Ser Ser Arg Ala Arg Pro Ser Ser Gln Gly Glu Arg Trp Trp
                330                 335                 340

ggc cca cgc tgc ccg gat acc cac ccc aca tcc cca cca gcg gac agg       1231
Gly Pro Arg Cys Pro Asp Thr His Pro Thr Ser Pro Pro Ala Asp Arg
            345                 350                 355

gca gct atg cct cct ctg cca tcg cag gca tgg tgg cag gaa gtg aat       1279
Ala Ala Met Pro Pro Leu Pro Ser Gln Ala Trp Trp Gln Glu Val Asn
        360                 365                 370

act ctg gca atg cct atg gcc aca ccc cct act cct cct aca gcg agg       1327
Thr Leu Ala Met Pro Met Ala Thr Pro Pro Thr Pro Pro Thr Ala Arg
    375                 380                 385

cct ggg gct tcc cca act cca gct tgc tgagttcccc atattattac             1374
Pro Gly Ala Ser Pro Thr Pro Ala Cys
390                 395

agttccacat caaggccgag tgcaccgccc accactgcca cggcctttga ccatctgtag     1434

ttgccatggg gacagtg                                                    1451
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Gly Gly Ala Phe Val Asn Gly Arg Pro Leu Pro Glu Val Val Arg Gln
            20                  25                  30
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Arg Ile Val Asp Leu Ala His Gln Gly Val Arg Pro Cys Asp Ile Ser
35 40 45

Arg Gln Leu Arg Val Ser His Gly Cys Val Ser Lys Ile Leu Gly Arg
50 55 60

Tyr Tyr Glu Thr Gly Ser Ile Arg Pro Gly Val Ile Gly Gly Ser Lys
65 70 75 80

Pro Lys Val Ala Thr Pro Lys Val Val Glu Lys Ile Gly Asp Tyr Lys
85 90 95

Arg Gln Asn Pro Thr Met Phe Ala Trp Glu Ile Arg Asp Arg Leu Leu
100 105 110

Ala Glu Gly Val Cys Asp Asn Asp Thr Val Pro Ser Val Ser Ser Ile
115 120 125

Asn Arg Ile Ile Arg Thr Lys Val Gln Gln Pro Phe Asn Leu Pro Met
130 135 140

Asp Ser Cys Val Ala Thr Lys Ser Leu Ser Pro Gly His Thr Leu Ile
145 150 155 160

Pro Ser Ser Ala Val Thr Pro Pro Glu Ser Pro Gln Ser Asp Ser Leu
165 170 175

Gly Ser Thr Tyr Ser Ile Asn Gly Leu Leu Gly Ile Ala Gln Pro Gly
180 185 190

Ser Asp Lys Arg Lys Met Asp Asp Ser Asp Gln Asp Ser Cys Arg Leu
195 200 205

Ser Ile Asp Ser Gln Ser Ser Ser Ser Gly Pro Arg Lys His Leu Arg
210 215 220

Thr Asp Ala Phe Ser Gln His His Leu Glu Pro Leu Glu Cys Pro Phe
225 230 235 240

Glu Arg Gln His Tyr Pro Glu Ala Tyr Ala Ser Pro Ser His Thr Lys
245 250 255

Gly Glu Gln Gly Leu Tyr Pro Leu Pro Leu Leu Asn Ser Thr Leu Asp
260 265 270

Asp Gly Lys Ala Thr Leu Thr Pro Ser Asn Thr Pro Leu Gly Arg Asn
275 280 285

Leu Ser Thr His Gln Thr Tyr Pro Val Val Ala Ala Pro Pro Phe Trp
290 295 300

Ile Cys Ser Lys Ser Ala Pro Gly Ser Arg Pro Ser Met Pro Phe Pro
305 310 315 320

Met Leu Pro Pro Cys Thr Gly Ser Ser Arg Ala Arg Pro Ser Ser Gln
325 330 335

Gly Glu Arg Trp Trp Gly Pro Arg Cys Pro Asp Thr His Pro Thr Ser
340 345 350

Pro Pro Ala Asp Arg Ala Ala Met Pro Pro Leu Pro Ser Gln Ala Trp
355 360 365

Trp Gln Glu Val Asn Thr Leu Ala Met Pro Met Ala Thr Pro Pro Thr
370 375 380

Pro Pro Thr Ala Arg Pro Gly Ala Ser Pro Thr Pro Ala Cys
385 390 395

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<211> 326

<212> DNA

<213> AI301558 EST

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gagattagaa actaaacaaa aaggggggcg gggaaggaaa ttctagagtc gttctggttt 120

gcaggtggtt gcggtcacaa agagaaatca tcaagaatgt tcacttggca tgtgtgaaag 180

attcaggggg tctgcagctg tttagtgttg atgcagttgg gtcaaaagag tatcatgtta 240

gtcttctgtg ggttttaggg agggattatg gagcctccct cccaccccac tggctttctt 300

gtgtcacagc ctttatttct actccg 326

<210> 46

<211> 1534

<212> DNA

<213> NM_018000 FLJ10116

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<221> CDS

<222> (267)..(938)

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gtgatgcgcg cggaccagcc cgcgacgccc gggctgccgc tgtccccgca cctggacgct     180

ggcgcggtgg ccgcgcccca gcctcgatcg ctcgccgcgg cgactcggcc ccaggcttcc     240

ggcgccggtg gggccctcg ctctcc atg ggg ctg agg gac tgg ctg aga acc      293
                            Met Gly Leu Arg Asp Trp Leu Arg Thr
                            1               5

gtg tgc tgc tgc tgc cgg tgc gag tgc ttg gag gag cgc gcc ctg cct      341
Val Cys Cys Cys Cys Arg Cys Glu Cys Leu Glu Glu Arg Ala Leu Pro
10                  15                  20                  25

gag aag gag ccc ctc gtc agt gat aac aat cca tat tcc tca ttt gga      389
Glu Lys Glu Pro Leu Val Ser Asp Asn Asn Pro Tyr Ser Ser Phe Gly
                30                  35                  40

gca act ctg gtg agg gat gat gag aag aat tta tgg agt atg ccc cat      437
Ala Thr Leu Val Arg Asp Asp Glu Lys Asn Leu Trp Ser Met Pro His
            45                  50                  55

gat gtg tcc cac aca gag gca gac gac gac aga acc ctg tac aat ttg      485
Asp Val Ser His Thr Glu Ala Asp Asp Asp Arg Thr Leu Tyr Asn Leu
        60                  65                  70

ata gtc att cgt aat cag cag gcc aaa gac tca gag gag tgg cag aag      533
Ile Val Ile Arg Asn Gln Gln Ala Lys Asp Ser Glu Glu Trp Gln Lys
    75                  80                  85

ctc aac tat gat atc cat acc ctg cgg cag gtt cga agg gaa gta aga      581
Leu Asn Tyr Asp Ile His Thr Leu Arg Gln Val Arg Arg Glu Val Arg
90                  95                  100                 105

aac aga tgg aag tgc atc tta gaa gat tta ggt ttt caa aag gaa gct      629
Asn Arg Trp Lys Cys Ile Leu Glu Asp Leu Gly Phe Gln Lys Glu Ala
                110                 115                 120

gac tct ttg ttg tca gtg act aaa ctc agc acc atc agt gat tct aaa      677
Asp Ser Leu Leu Ser Val Thr Lys Leu Ser Thr Ile Ser Asp Ser Lys
            125                 130                 135

aac aca agg aaa gct cga gag atg ttg tta aaa ctg gct gaa gaa acc      725
Asn Thr Arg Lys Ala Arg Glu Met Leu Leu Lys Leu Ala Glu Glu Thr
        140                 145                 150

agt att ttc cca aca agt tgg gag ctc tca gag aga tat ctc ttt gtt      773
Ser Ile Phe Pro Thr Ser Trp Glu Leu Ser Glu Arg Tyr Leu Phe Val
    155                 160                 165

gtg gac cgt ctc att gca ctt gat gct gca gaa gag ttc ttt aag ctt      821
Val Asp Arg Leu Ile Ala Leu Asp Ala Ala Glu Glu Phe Phe Lys Leu
170                 175                 180                 185

gct cgt cga act tac ccc aag aag cct ggg gtt cca tgc ctg gca gat      869
Ala Arg Arg Thr Tyr Pro Lys Lys Pro Gly Val Pro Cys Leu Ala Asp
                190                 195                 200

ggc cag aaa gaa ctg cac ctg tgg ggg gac ctc tca tgc aga ctt gca      917
Gly Gln Lys Glu Leu His Leu Trp Gly Asp Leu Ser Cys Arg Leu Ala
            205                 210                 215

cat atg cag gga gta ttg cac tgaagatctt tgctggacct tcttctcttc          968
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His Met Gln Gly Val Leu His
220

agaagataat tttcaaaagg gagcaatgct gtgaatgcag cttgcttctc tctacagatt 1028

gagaagtcca gcttcaaaag ttacttgcca cttaagcaag gaacttgtca agagatcatg 1088

gttcatgtta ctgaaaagac tttaaggatt tgtaaggtta atccatagat tgctgagaac 1148

aatggaaata tttttatttt tacagatttt gcacttctga attcaggtta aaaactaact 1208

tgtatttagt ctgcttagag gactgtgact tgaaaatttt tatataccaa tgagcttttt 1268

ggtagcgtcc acaatgttta aaatatttca taggcgagat ccgtgttctc catttattaa 1328

tgcattgtag accaatttaa ctgctgtgtt tcaggaaaat tcttcctagt ttaataagca 1388

agctaaaagt tttatttttt atatttagtg cttaatcttt gcctcatgtt atgtaaaatt 1448

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Met Gly Leu Arg Asp Trp Leu Arg Thr Val Cys Cys Cys Cys Arg Cys
1 5 10 15

Glu Cys Leu Glu Glu Arg Ala Leu Pro Glu Lys Glu Pro Leu Val Ser
20 25 30

Asp Asn Asn Pro Tyr Ser Ser Phe Gly Ala Thr Leu Val Arg Asp Asp
35 40 45

Glu Lys Asn Leu Trp Ser Met Pro His Asp Val Ser His Thr Glu Ala
50 55 60

Asp Asp Asp Arg Thr Leu Tyr Asn Leu Ile Val Ile Arg Asn Gln Gln
65 70 75 80

Ala Lys Asp Ser Glu Glu Trp Gln Lys Leu Asn Tyr Asp Ile His Thr
85 90 95

Leu Arg Gln Val Arg Arg Glu Val Arg Asn Arg Trp Lys Cys Ile Leu
100 105 110

Glu Asp Leu Gly Phe Gln Lys Glu Ala Asp Ser Leu Leu Ser Val Thr
115 120 125

```
Lys Leu Ser Thr Ile Ser Asp Ser Lys Asn Thr Arg Lys Ala Arg Glu
    130                 135                 140

Met Leu Leu Lys Leu Ala Glu Glu Thr Ser Ile Phe Pro Thr Ser Trp
145                 150                 155                 160

Glu Leu Ser Glu Arg Tyr Leu Phe Val Val Asp Arg Leu Ile Ala Leu
                165                 170                 175

Asp Ala Ala Glu Glu Phe Phe Lys Leu Ala Arg Arg Thr Tyr Pro Lys
            180                 185                 190

Lys Pro Gly Val Pro Cys Leu Ala Asp Gly Gln Lys Glu Leu His Leu
        195                 200                 205

Trp Gly Asp Leu Ser Cys Arg Leu Ala His Met Gln Gly Val Leu His
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<212> DNA

<213> NM_144724 FLJ30532

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<222> (71)..(1441)

<223>

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aaaatcacaa atg tca aat gat gga aga tcc agg aat cgg gac agg cgc        109
           Met Ser Asn Asp Gly Arg Ser Arg Asn Arg Asp Arg Arg
           1               5                   10

tac gat gag gtc cca agc gac ctg ccc tat caa gat acc acc ata aga       157
Tyr Asp Glu Val Pro Ser Asp Leu Pro Tyr Gln Asp Thr Thr Ile Arg
    15                  20                  25

acc cac cca att ctt cat gac agt gag cgg gca gtg agc gct gat ccc       205
Thr His Pro Ile Leu His Asp Ser Glu Arg Ala Val Ser Ala Asp Pro
30                  35                  40                  45

ttg cca cca ccc cct ctc cca tta cag cca cca ttc ggc cca gac ttc       253
Leu Pro Pro Pro Pro Leu Pro Leu Gln Pro Pro Phe Gly Pro Asp Phe
                50                  55                  60

tac tca agt gac aca gaa gaa cca gct ata gcg cca gat ctc aaa cca       301
Tyr Ser Ser Asp Thr Glu Glu Pro Ala Ile Ala Pro Asp Leu Lys Pro
            65                  70                  75

gta agg cgc ttt gtc cct gac tcc tgg aag aac ttt ttc aga ggg aag       349
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Val Arg Arg Phe Val Pro Asp Ser Trp Lys Asn Phe Phe Arg Gly Lys
        80                  85                  90

aaa aag gac ccc gaa tgg gat aag ccg gtg tct gat atc agg tac atc      397
Lys Lys Asp Pro Glu Trp Asp Lys Pro Val Ser Asp Ile Arg Tyr Ile
    95                  100                 105

tcc gat gga gtg gag tgt tca cca cca gcc tct cca gca aga cca aac      445
Ser Asp Gly Val Glu Cys Ser Pro Pro Ala Ser Pro Ala Arg Pro Asn
110                 115                 120                 125

cac cgt tcg ccc ctc aac tcc tgc aaa gat ccc tac gga ggg tca gaa      493
His Arg Ser Pro Leu Asn Ser Cys Lys Asp Pro Tyr Gly Gly Ser Glu
                130                 135                 140

gga acc ttt agt tcc cgg aaa gag gct gac gca gtg ttt ccc cgg gat      541
Gly Thr Phe Ser Ser Arg Lys Glu Ala Asp Ala Val Phe Pro Arg Asp
            145                 150                 155

ccc tat gga tct cta gac cga cac aca caa aca gtt cga aca tac agt      589
Pro Tyr Gly Ser Leu Asp Arg His Thr Gln Thr Val Arg Thr Tyr Ser
        160                 165                 170

gag aag gtg gag gag tat aac ctg aga tac tcc tac atg aag tcg tgg      637
Glu Lys Val Glu Glu Tyr Asn Leu Arg Tyr Ser Tyr Met Lys Ser Trp
    175                 180                 185

gca ggc ctg ctg aga ata ctg ggt gtg gtg gag ctg ctt ttg ggg gcc      685
Ala Gly Leu Leu Arg Ile Leu Gly Val Val Glu Leu Leu Leu Gly Ala
190                 195                 200                 205

ggt gtc ttt gct tgt gtc aca gct tac att cac aag gac agt gag tgg      733
Gly Val Phe Ala Cys Val Thr Ala Tyr Ile His Lys Asp Ser Glu Trp
                210                 215                 220

tac aac ttg ttt gga tat tca caa ccg tat ggc atg gga ggc gtt ggt      781
Tyr Asn Leu Phe Gly Tyr Ser Gln Pro Tyr Gly Met Gly Gly Val Gly
            225                 230                 235

gga ttg ggc agt atg tat ggg ggc tat tac tac act ggc cct aag acc      829
Gly Leu Gly Ser Met Tyr Gly Gly Tyr Tyr Tyr Thr Gly Pro Lys Thr
        240                 245                 250

cct ttt gta ctc gtg gtt gct gga tta gct tgg atc acc acc att att      877
Pro Phe Val Leu Val Val Ala Gly Leu Ala Trp Ile Thr Thr Ile Ile
    255                 260                 265

att ctg gtt ctt ggc atg tcc atg tat tac cgg acc att ctt ctg gac      925
Ile Leu Val Leu Gly Met Ser Met Tyr Tyr Arg Thr Ile Leu Leu Asp
270                 275                 280                 285

tct aat tgg tgg ccc cta act gaa ttt gga att aac gtt gcc ttg ttt      973
Ser Asn Trp Trp Pro Leu Thr Glu Phe Gly Ile Asn Val Ala Leu Phe
                290                 295                 300

att ttg tat atg gcc gca gcc ata gtc tat gtg aat gat acc aac cga      1021
Ile Leu Tyr Met Ala Ala Ala Ile Val Tyr Val Asn Asp Thr Asn Arg
            305                 310                 315

ggt ggc ctc tgc tac tat ccg tta ttt aat aca cca gtg aat gca gtg      1069
Gly Gly Leu Cys Tyr Tyr Pro Leu Phe Asn Thr Pro Val Asn Ala Val
        320                 325                 330

ttc tgc cgg gta gaa gga gga cag ata gct gca atg atc ttc ctg ttt      1117
Phe Cys Arg Val Glu Gly Gly Gln Ile Ala Ala Met Ile Phe Leu Phe
    335                 340                 345

gtc acc atg ata gtt tat ctc att agt gct ttg gtt tgc cta aag tta      1165
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Val Thr Met Ile Val Tyr Leu Ile Ser Ala Leu Val Cys Leu Lys Leu
350                 355                 360                 365

tgg agg cat gag gca gct cgg aga cat aga gaa tat atg gaa caa cag      1213
Trp Arg His Glu Ala Ala Arg Arg His Arg Glu Tyr Met Glu Gln Gln
                370                 375                 380

gag ata aat gag cca tca ttg tca tcg aaa agg aaa atg tgt gaa atg      1261
Glu Ile Asn Glu Pro Ser Leu Ser Ser Lys Arg Lys Met Cys Glu Met
            385                 390                 395

gcc acc agt ggt gac aga caa aga gac tca gaa gtt aat ttc aag gaa      1309
Ala Thr Ser Gly Asp Arg Gln Arg Asp Ser Glu Val Asn Phe Lys Glu
        400                 405                 410

ctg aga aca gca aaa atg aaa cct gaa cta ctg agt gga cac atc ccc      1357
Leu Arg Thr Ala Lys Met Lys Pro Glu Leu Leu Ser Gly His Ile Pro
    415                 420                 425

cca cgc cca gct aat ttt ttt gta ttt tta gta gag atg ggg ttt cac      1405
Pro Arg Pro Ala Asn Phe Phe Val Phe Leu Val Glu Met Gly Phe His
430                 435                 440                 445

cgt gtt agc cag gat gat ctc gat ctc ctg acc tca tgatccaccc           1451
Arg Val Ser Gln Asp Asp Leu Asp Leu Leu Thr Ser
                450                 455

gcctcagcct cccaaagtgt tgggattaca ggcgtgagtc accgcgccca gctggtattg    1511

cttttctatt ccctttggac atacatgcta cagtcccaca atgtagcatt tccttggaaa    1571

ctcccttttt tttttttttt gagatggagt ttcgctcttg ttgcccaggc tggagtacag    1631

tggtatgatc ttggctcact gcagcctctg cctcctgggt tcaagcgatt ctcctgcctc    1691

tgcctcccaa gtagctggga ttacaggcac ccaccaccat gcccagctaa tttttttgtat   1751

ttttagtaga gacaggattt cactatgttg gccaggttgg tctcaagctc ctgacctcag    1811

atgatctacc agcctcggcc ttctgaagtg ctgggattca ggtgtgagcc actgtgccca    1871

gcagggatgc ttcatctttc taagaattat cttggctttg gactttattc ataaatgttt    1931

tatttctgtt agtatgaaca atagactgcc ttaacaaagt ttttttttaa acaaaatcgt    1991

tcttgttgga ttttattcag cagcatctat catgtagata aattcccagg tgtagcatta    2051

cagcttctga ctaatatagc tgccattcag acaattaatg ttcaaagagt tttctaaagt    2111

gataaaacca aagaaaagca tgtggaaaag cagaagctta gaaagttgtg gtcactgaat    2171

gcactccctg gtttttattt gtcagtgaaa tctttatgca ttcattgtta atattttaat    2231

tccatggctt tgtaggctgt gctgtgtctg aaggggtaac acctagggaa acatgaggcc    2291

ccttatggga ccccccaaat ggaacaactt cactttctct tttatgtatt gagccctgtg    2351

ttaacatttc acttaagaag agcaccagtg cttt                                2385
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<213> NM_144724 FLJ30532

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Val Pro Ser Asp Leu Pro Tyr Gln Asp Thr Thr Ile Arg Thr His Pro
20 25 30

Ile Leu His Asp Ser Glu Arg Ala Val Ser Ala Asp Pro Leu Pro Pro
35 40 45

Pro Pro Leu Pro Leu Gln Pro Pro Phe Gly Pro Asp Phe Tyr Ser Ser
50 55 60

Asp Thr Glu Glu Pro Ala Ile Ala Pro Asp Leu Lys Pro Val Arg Arg
65 70 75 80

Phe Val Pro Asp Ser Trp Lys Asn Phe Phe Arg Gly Lys Lys Lys Asp
85 90 95

Pro Glu Trp Asp Lys Pro Val Ser Asp Ile Arg Tyr Ile Ser Asp Gly
100 105 110

Val Glu Cys Ser Pro Pro Ala Ser Pro Ala Arg Pro Asn His Arg Ser
115 120 125

Pro Leu Asn Ser Cys Lys Asp Pro Tyr Gly Gly Ser Glu Gly Thr Phe
130 135 140

Ser Ser Arg Lys Glu Ala Asp Ala Val Phe Pro Arg Asp Pro Tyr Gly
145 150 155 160

Ser Leu Asp Arg His Thr Gln Thr Val Arg Thr Tyr Ser Glu Lys Val
165 170 175

Glu Glu Tyr Asn Leu Arg Tyr Ser Tyr Met Lys Ser Trp Ala Gly Leu
180 185 190

Leu Arg Ile Leu Gly Val Val Glu Leu Leu Leu Gly Ala Gly Val Phe
195 200 205

Ala Cys Val Thr Ala Tyr Ile His Lys Asp Ser Glu Trp Tyr Asn Leu
210 215 220

Phe Gly Tyr Ser Gln Pro Tyr Gly Met Gly Gly Val Gly Gly Leu Gly
225 230 235 240

Ser Met Tyr Gly Gly Tyr Tyr Tyr Thr Gly Pro Lys Thr Pro Phe Val
245 250 255

Leu Val Val Ala Gly Leu Ala Trp Ile Thr Thr Ile Ile Ile Leu Val
260 265 270

Leu Gly Met Ser Met Tyr Tyr Arg Thr Ile Leu Leu Asp Ser Asn Trp
275 280 285

Trp Pro Leu Thr Glu Phe Gly Ile Asn Val Ala Leu Phe Ile Leu Tyr
290 295 300

Met Ala Ala Ala Ile Val Tyr Val Asn Asp Thr Asn Arg Gly Gly Leu
305 310 315 320

Cys Tyr Tyr Pro Leu Phe Asn Thr Pro Val Asn Ala Val Phe Cys Arg
325 330 335

Val Glu Gly Gly Gln Ile Ala Ala Met Ile Phe Leu Phe Val Thr Met
340 345 350

Ile Val Tyr Leu Ile Ser Ala Leu Val Cys Leu Lys Leu Trp Arg His
355 360 365

Glu Ala Ala Arg Arg His Arg Glu Tyr Met Glu Gln Gln Glu Ile Asn
370 375 380

Glu Pro Ser Leu Ser Ser Lys Arg Lys Met Cys Glu Met Ala Thr Ser
385 390 395 400

Gly Asp Arg Gln Arg Asp Ser Glu Val Asn Phe Lys Glu Leu Arg Thr
405 410 415

Ala Lys Met Lys Pro Glu Leu Leu Ser Gly His Ile Pro Pro Arg Pro
420 425 430

Ala Asn Phe Phe Val Phe Leu Val Glu Met Gly Phe His Arg Val Ser
435 440 445

Gln Asp Asp Leu Asp Leu Leu Thr Ser
450 455

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acc atg gct ccc tgg cct gaa ttg gga gat gcc cag ccc aac ccc gat        108
    Met Ala Pro Trp Pro Glu Leu Gly Asp Ala Gln Pro Asn Pro Asp
    1               5                   10                  15

aag tac ctc gaa ggg gcc gca ggt cag cag ccc act gcc cct gat aaa        156
Lys Tyr Leu Glu Gly Ala Ala Gly Gln Gln Pro Thr Ala Pro Asp Lys
                20                  25                  30

agc aaa gag acc aac aaa aca gat aac act gag gca cct gta acc aag        204
Ser Lys Glu Thr Asn Lys Thr Asp Asn Thr Glu Ala Pro Val Thr Lys
            35                  40                  45

att gaa ctt ctg ccg tcc tac tcc acg gct aca ctg ata gat gag ccc        252
Ile Glu Leu Leu Pro Ser Tyr Ser Thr Ala Thr Leu Ile Asp Glu Pro
        50                  55                  60

act gag gtg gat gac ccc tgg aac cta ccc act ctt cag gac tcg ggg        300
Thr Glu Val Asp Asp Pro Trp Asn Leu Pro Thr Leu Gln Asp Ser Gly
    65                  70                  75

atc aag tgg tca gag aga gac acc aaa ggg aag att ctc tgt ttc ttc        348
Ile Lys Trp Ser Glu Arg Asp Thr Lys Gly Lys Ile Leu Cys Phe Phe
80                  85                  90                  95

caa ggg att ggg aga ttg att tta ctt ctc gga ttt ctc tac ttt ttc        396
Gln Gly Ile Gly Arg Leu Ile Leu Leu Leu Gly Phe Leu Tyr Phe Phe
                100                 105                 110

gtg tgc tcc ctg gat att ctt agt agc gcc ttc cag ctg gtt gga gga        444
Val Cys Ser Leu Asp Ile Leu Ser Ser Ala Phe Gln Leu Val Gly Gly
            115                 120                 125

aaa atg gca gga cag ttc ttc agc aac agc tct att atg tcc aac cct        492
Lys Met Ala Gly Gln Phe Phe Ser Asn Ser Ser Ile Met Ser Asn Pro
        130                 135                 140

ttg ttg ggg ctg gtg atc ggg gtg ctg gtg acc gtc ttg gtg cag agc        540
Leu Leu Gly Leu Val Ile Gly Val Leu Val Thr Val Leu Val Gln Ser
    145                 150                 155

tcc agc acc tca acg tcc atc gtt gtc agc atg gtg tcc tct tca ttg        588
Ser Ser Thr Ser Thr Ser Ile Val Val Ser Met Val Ser Ser Ser Leu
160                 165                 170                 175

ctc act gtt cgg gct gcc atc ccc att atc atg ggg gcc aac att gga        636
Leu Thr Val Arg Ala Ala Ile Pro Ile Ile Met Gly Ala Asn Ile Gly
                180                 185                 190

acg tca atc acc aac act att gtt gcg ctc atg cag gtg gga gat cgg        684
Thr Ser Ile Thr Asn Thr Ile Val Ala Leu Met Gln Val Gly Asp Arg
            195                 200                 205

agt gag ttc aga aga gct ttt gca gga gcc act gtc cat gac ttc ttc        732
Ser Glu Phe Arg Arg Ala Phe Ala Gly Ala Thr Val His Asp Phe Phe
        210                 215                 220

aac tgg ctg tcc gtg ttg gtg ctc ttg ccc gtg gag gtg gcc acc cat        780
Asn Trp Leu Ser Val Leu Val Leu Leu Pro Val Glu Val Ala Thr His
    225                 230                 235
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tac ctc gag atc ata acc cag ctt ata gtg gag agc ttc cac ttc aag      828
Tyr Leu Glu Ile Ile Thr Gln Leu Ile Val Glu Ser Phe His Phe Lys
240                 245                 250                 255

aat gga gaa gat gcc cca gat ctt ctg aaa gtc atc act aag ccc ttc      876
Asn Gly Glu Asp Ala Pro Asp Leu Leu Lys Val Ile Thr Lys Pro Phe
                260                 265                 270

aca aag ctc att gtc cag ctg gat aaa aaa gtt atc agc caa att gca      924
Thr Lys Leu Ile Val Gln Leu Asp Lys Lys Val Ile Ser Gln Ile Ala
            275                 280                 285

atg aac gat gaa aaa gcg aaa aac aag agt ctt gtc aag att tgg tgc      972
Met Asn Asp Glu Lys Ala Lys Asn Lys Ser Leu Val Lys Ile Trp Cys
        290                 295                 300

aaa act ttt acc aac aag acc cag att aac gtc act gtt ccc tcg act     1020
Lys Thr Phe Thr Asn Lys Thr Gln Ile Asn Val Thr Val Pro Ser Thr
    305                 310                 315

gct aac tgc acc tcc cct tcc ctc tgt tgg acg gat ggc atc caa aac     1068
Ala Asn Cys Thr Ser Pro Ser Leu Cys Trp Thr Asp Gly Ile Gln Asn
320                 325                 330                 335

tgg acc atg aag aat gtg acc tac aag gag aac atc gcc aaa tgc cag     1116
Trp Thr Met Lys Asn Val Thr Tyr Lys Glu Asn Ile Ala Lys Cys Gln
                340                 345                 350

cat atc ttt gtg aat ttc cac ctc ccg gat ctt gct gtg ggc acc atc     1164
His Ile Phe Val Asn Phe His Leu Pro Asp Leu Ala Val Gly Thr Ile
            355                 360                 365

ttg ctc ata ctc tcc ctg ctg gtc ctc tgt ggt tgc ctg atc atg att     1212
Leu Leu Ile Leu Ser Leu Leu Val Leu Cys Gly Cys Leu Ile Met Ile
        370                 375                 380

gtc aag atc ctg ggc tct gtg ctc aag ggg cag gtc gcc act gtc atc     1260
Val Lys Ile Leu Gly Ser Val Leu Lys Gly Gln Val Ala Thr Val Ile
    385                 390                 395

aag aag acc atc aac act gat ttc ccc ttt ccc ttt gca tgg ttg act     1308
Lys Lys Thr Ile Asn Thr Asp Phe Pro Phe Pro Phe Ala Trp Leu Thr
400                 405                 410                 415

ggc tac ctg gcc atc ctc gtc ggg gca ggc atg acc ttc atc gta cag     1356
Gly Tyr Leu Ala Ile Leu Val Gly Ala Gly Met Thr Phe Ile Val Gln
                420                 425                 430

agc agc tct gtg ttc acg tcg gcc ttg acc ccc ctg att gga atc ggc     1404
Ser Ser Ser Val Phe Thr Ser Ala Leu Thr Pro Leu Ile Gly Ile Gly
            435                 440                 445

gtg ata acc att gag agg gct tat cca ctc acg ctg ggc tcc aac atc     1452
Val Ile Thr Ile Glu Arg Ala Tyr Pro Leu Thr Leu Gly Ser Asn Ile
        450                 455                 460

ggc acc acc acc acc gcc atc ctg gcc gcc tta gcc agc cct ggc aat     1500
Gly Thr Thr Thr Thr Ala Ile Leu Ala Ala Leu Ala Ser Pro Gly Asn
    465                 470                 475

gca ttg agg agt tca ctc cag atc gcc ctg tgc cac ttt ttc ttc aac     1548
Ala Leu Arg Ser Ser Leu Gln Ile Ala Leu Cys His Phe Phe Phe Asn
480                 485                 490                 495

atc tcc ggc atc ttg ctg tgg tac ccg atc ccg ttc act cgc ctg ccc     1596
Ile Ser Gly Ile Leu Leu Trp Tyr Pro Ile Pro Phe Thr Arg Leu Pro
                500                 505                 510
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atc cgc atg gcc aag ggg ctg ggc aac atc tct gcc aag tat cgc tgg      1644
Ile Arg Met Ala Lys Gly Leu Gly Asn Ile Ser Ala Lys Tyr Arg Trp
            515                 520                 525

ttc gcc gtc ttc tac ctg atc atc ttc ttc ttc ctg atc ccg ctg acg      1692
Phe Ala Val Phe Tyr Leu Ile Ile Phe Phe Phe Leu Ile Pro Leu Thr
        530                 535                 540

gtg ttt ggc ctc tcg ctg gcc ggc tgg cgg gtg ctg gtt ggt gtc ggg      1740
Val Phe Gly Leu Ser Leu Ala Gly Trp Arg Val Leu Val Gly Val Gly
    545                 550                 555

gtt ccc gtc gtc ttc atc atc atc ctg gta ctg tgc ctc cga ctc ctg      1788
Val Pro Val Val Phe Ile Ile Ile Leu Val Leu Cys Leu Arg Leu Leu
560                 565                 570                 575

cag tct cgc tgc cca cgc gtc ctg ccg aag aaa ctc cag aac tgg aac      1836
Gln Ser Arg Cys Pro Arg Val Leu Pro Lys Lys Leu Gln Asn Trp Asn
                580                 585                 590

ttc ctg ccg ctg tgg atg cgc tcg ctg aag ccc tgg gat gcc gtc gtc      1884
Phe Leu Pro Leu Trp Met Arg Ser Leu Lys Pro Trp Asp Ala Val Val
            595                 600                 605

tcc aag ttc acc ggc tgc ttc cag atg cgc tgc tgc tac tgc tgc cgc      1932
Ser Lys Phe Thr Gly Cys Phe Gln Met Arg Cys Cys Tyr Cys Cys Arg
        610                 615                 620

gtg tgc tgc cgc gcg tgc tgc ttg ctg tgt ggc tgc ccc aag tgc tgc      1980
Val Cys Cys Arg Ala Cys Cys Leu Leu Cys Gly Cys Pro Lys Cys Cys
    625                 630                 635

cgc tgc agc aag tgc tgc gag gac ttg gag gag gcg cag gag ggg cag      2028
Arg Cys Ser Lys Cys Cys Glu Asp Leu Glu Glu Ala Gln Glu Gly Gln
640                 645                 650                 655

gat gtc cct gtc aag gct cct gag acc ttt gat aac ata acc att agc      2076
Asp Val Pro Val Lys Ala Pro Glu Thr Phe Asp Asn Ile Thr Ile Ser
                660                 665                 670

aga gag gct cag ggt gag gtc cct gcc tcg gac tca aag acc gaa tgc      2124
Arg Glu Ala Gln Gly Glu Val Pro Ala Ser Asp Ser Lys Thr Glu Cys
            675                 680                 685

acg gcc ttg taggggacgc cccagattgt cagggatggg gggatggtcc              2173
Thr Ala Leu
        690

ttgagttttg catgctctcc tccctcccac ttctgcaccc tttcaccacc tcgaggagat   2233

ttgctcccca ttagcgaatg aaattgatgc agtcctaaaa aaaaaaa                  2280
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20 25 30

Lys Glu Thr Asn Lys Thr Asp Asn Thr Glu Ala Pro Val Thr Lys Ile
35 40 45

Glu Leu Leu Pro Ser Tyr Ser Thr Ala Thr Leu Ile Asp Glu Pro Thr
50 55 60

Glu Val Asp Asp Pro Trp Asn Leu Pro Thr Leu Gln Asp Ser Gly Ile
65 70 75 80

Lys Trp Ser Glu Arg Asp Thr Lys Gly Lys Ile Leu Cys Phe Phe Gln
85 90 95

Gly Ile Gly Arg Leu Ile Leu Leu Leu Gly Phe Leu Tyr Phe Phe Val
100 105 110

Cys Ser Leu Asp Ile Leu Ser Ser Ala Phe Gln Leu Val Gly Gly Lys
115 120 125

Met Ala Gly Gln Phe Phe Ser Asn Ser Ser Ile Met Ser Asn Pro Leu
130 135 140

Leu Gly Leu Val Ile Gly Val Leu Val Thr Val Leu Val Gln Ser Ser
145 150 155 160

Ser Thr Ser Thr Ser Ile Val Val Ser Met Val Ser Ser Ser Leu Leu
165 170 175

Thr Val Arg Ala Ala Ile Pro Ile Ile Met Gly Ala Asn Ile Gly Thr
180 185 190

Ser Ile Thr Asn Thr Ile Val Ala Leu Met Gln Val Gly Asp Arg Ser
195 200 205

Glu Phe Arg Arg Ala Phe Ala Gly Ala Thr Val His Asp Phe Phe Asn
210 215 220

Trp Leu Ser Val Leu Val Leu Leu Pro Val Glu Val Ala Thr His Tyr
225 230 235 240

Leu Glu Ile Ile Thr Gln Leu Ile Val Glu Ser Phe His Phe Lys Asn
245 250 255

Gly Glu Asp Ala Pro Asp Leu Leu Lys Val Ile Thr Lys Pro Phe Thr
260 265 270

Lys Leu Ile Val Gln Leu Asp Lys Lys Val Ile Ser Gln Ile Ala Met

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        275                 280                 285

Asn Asp Glu Lys Ala Lys Asn Lys Ser Leu Val Lys Ile Trp Cys Lys
    290                 295                 300

Thr Phe Thr Asn Lys Thr Gln Ile Asn Val Thr Val Pro Ser Thr Ala
305                 310                 315                 320

Asn Cys Thr Ser Pro Ser Leu Cys Trp Thr Asp Gly Ile Gln Asn Trp
                325                 330                 335

Thr Met Lys Asn Val Thr Tyr Lys Glu Asn Ile Ala Lys Cys Gln His
            340                 345                 350

Ile Phe Val Asn Phe His Leu Pro Asp Leu Ala Val Gly Thr Ile Leu
        355                 360                 365

Leu Ile Leu Ser Leu Leu Val Leu Cys Gly Cys Leu Ile Met Ile Val
    370                 375                 380

Lys Ile Leu Gly Ser Val Leu Lys Gly Gln Val Ala Thr Val Ile Lys
385                 390                 395                 400

Lys Thr Ile Asn Thr Asp Phe Pro Phe Pro Phe Ala Trp Leu Thr Gly
                405                 410                 415

Tyr Leu Ala Ile Leu Val Gly Ala Gly Met Thr Phe Ile Val Gln Ser
            420                 425                 430

Ser Ser Val Phe Thr Ser Ala Leu Thr Pro Leu Ile Gly Ile Gly Val
        435                 440                 445

Ile Thr Ile Glu Arg Ala Tyr Pro Leu Thr Leu Gly Ser Asn Ile Gly
    450                 455                 460

Thr Thr Thr Thr Ala Ile Leu Ala Ala Leu Ala Ser Pro Gly Asn Ala
465                 470                 475                 480

Leu Arg Ser Ser Leu Gln Ile Ala Leu Cys His Phe Phe Phe Asn Ile
                485                 490                 495

Ser Gly Ile Leu Leu Trp Tyr Pro Ile Pro Phe Thr Arg Leu Pro Ile
            500                 505                 510

Arg Met Ala Lys Gly Leu Gly Asn Ile Ser Ala Lys Tyr Arg Trp Phe
        515                 520                 525

Ala Val Phe Tyr Leu Ile Ile Phe Phe Phe Leu Ile Pro Leu Thr Val
    530                 535                 540

Phe Gly Leu Ser Leu Ala Gly Trp Arg Val Leu Val Gly Val Gly Val
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545 550 555 560

Pro Val Val Phe Ile Ile Ile Leu Val Leu Cys Leu Arg Leu Leu Gln
565 570 575

Ser Arg Cys Pro Arg Val Leu Pro Lys Lys Leu Gln Asn Trp Asn Phe
580 585 590

Leu Pro Leu Trp Met Arg Ser Leu Lys Pro Trp Asp Ala Val Val Ser
595 600 605

Lys Phe Thr Gly Cys Phe Gln Met Arg Cys Cys Tyr Cys Cys Arg Val
610 615 620

Cys Cys Arg Ala Cys Cys Leu Leu Cys Gly Cys Pro Lys Cys Cys Arg
625 630 635 640

Cys Ser Lys Cys Cys Glu Asp Leu Glu Glu Ala Gln Glu Gly Gln Asp
645 650 655

Val Pro Val Lys Ala Pro Glu Thr Phe Asp Asn Ile Thr Ile Ser Arg
660 665 670

Glu Ala Gln Gly Glu Val Pro Ala Ser Asp Ser Lys Thr Glu Cys Thr
675 680 685

Ala Leu
690

<210> 52

<211> 529

<212> DNA

<213> AW959311, DKFZp434J037, EST

<220>

<221> misc_feature

<222> (393)..(393)

<223> the residue at position 393 is A, T C or G

<400> 52
ctgtttcttc aatggttctc ttccctttc catcctccaa acctggcctg agcctcctga 60

agttgctgct gtgaatctga aagacttgaa aagcctccac ctgctgtgtg gacttcatct 120

caaggggccc agcctcctct ggactccacc ttggacctca gtgactcaga acttctgcct 180

ctaagctgct ctaaagtcca gactatggat gtgttctcta ggccttcagg actctagaat 240

gtccatattt atttttatgt tcttggcttt gtgttttagg aaaagtgaat cttgctgttt 300

tcaataatgt gaatgctatg ttctgggaaa atccactatg acatctaagt tttgtgtaca 360

gagagatatt tttgcaacta tttccacctt ctnccacaac cccccacact ccactccaca 420

ctcttgagtc tctttaccta atggtctcta cctaatggac cctcgtggcc aaaaagtcca 480

ttaaaccaga aaggtgattg gaaaaaaaaa aaaaaaaact cgaggggg 529

<210> 53

<211> 2100

<212> DNA

<213> AF111713 JAM1, junctional adhesion molecule 1

<220>

<221> CDS

<222> (287)..(1183)

<223>

<400> 53
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tggctggaga cggagtttcg ctcttgatgc ccagcaggct ggagtgcgat ggcgcgattt 120

cggctcactg caacctcctc ctcccagagg tacttctcag ccctctagct ccaactgaga 180

acccagccag tcaggaagtc gctacttcgg gaacaccaac caatcagggg gccgtcacct 240

gctgaaggag tccttcggcg gctgttgtgt cgggagcctg atcgcg atg ggg aca 295
Met Gly Thr
1

aag gcg caa gtc gag agg aaa ctg ttg tgc ctc ttc ata ttg gcg atc 343
Lys Ala Gln Val Glu Arg Lys Leu Leu Cys Leu Phe Ile Leu Ala Ile
5 10 15

ctg ttg tgc tcc ctg gca ttg ggc agt gtt aca gtg cac tct tct gaa 391
Leu Leu Cys Ser Leu Ala Leu Gly Ser Val Thr Val His Ser Ser Glu
20 25 30 35

cct gaa gtc aga att cct gag aat aat cct gtg aag ttg tcc tgt gcc 439
Pro Glu Val Arg Ile Pro Glu Asn Asn Pro Val Lys Leu Ser Cys Ala
40 45 50

tac tcg ggc ttt tct tct ccc cgt gtg gag tgg aag ttt gac caa gga 487
Tyr Ser Gly Phe Ser Ser Pro Arg Val Glu Trp Lys Phe Asp Gln Gly
55 60 65

gac acc acc aga ctc gtt tgc tat aat aac aag atc aca gct tcc tat 535
Asp Thr Thr Arg Leu Val Cys Tyr Asn Asn Lys Ile Thr Ala Ser Tyr
70 75 80

gag gac cgg gtg acc ttc ttg cca act ggt atc acc ttc aag tcc gtg 583
Glu Asp Arg Val Thr Phe Leu Pro Thr Gly Ile Thr Phe Lys Ser Val
85 90 95

```
aca cgg gaa gac act ggg aca tac act tgt atg gtc tct gag gaa ggc      631
Thr Arg Glu Asp Thr Gly Thr Tyr Thr Cys Met Val Ser Glu Glu Gly
100                 105                 110                 115

ggc aac agc tat ggg gag gtc aag gtc aag ctc atc gtg ctt gtg cct      679
Gly Asn Ser Tyr Gly Glu Val Lys Val Lys Leu Ile Val Leu Val Pro
                120                 125                 130

cca tcc aag cct aca gtt aac atc ccc tcc tct gcc acc att ggg aac      727
Pro Ser Lys Pro Thr Val Asn Ile Pro Ser Ser Ala Thr Ile Gly Asn
            135                 140                 145

cgg gca gtg ctg aca tgc tca gaa caa gat ggt tcc cca cct tct gaa      775
Arg Ala Val Leu Thr Cys Ser Glu Gln Asp Gly Ser Pro Pro Ser Glu
        150                 155                 160

tac acc tgg ttc aaa gat ggg ata gtg atg cct acg aat ccc aaa agc      823
Tyr Thr Trp Phe Lys Asp Gly Ile Val Met Pro Thr Asn Pro Lys Ser
    165                 170                 175

acc cgt gcc ttc agc aac tct tcc tat gtc ctg aat ccc aca aca gga      871
Thr Arg Ala Phe Ser Asn Ser Ser Tyr Val Leu Asn Pro Thr Thr Gly
180                 185                 190                 195

gag ctg gtc ttt gat ccc ctg tca gcc tct gat act gga gaa tac agc      919
Glu Leu Val Phe Asp Pro Leu Ser Ala Ser Asp Thr Gly Glu Tyr Ser
                200                 205                 210

tgt gag gca cgg aat ggg tat ggg aca ccc atg act tca aat gct gtg      967
Cys Glu Ala Arg Asn Gly Tyr Gly Thr Pro Met Thr Ser Asn Ala Val
            215                 220                 225

cgc atg gaa gct gtg gag cgg aat gtg ggg gtc atc gtg gca gcc gtc     1015
Arg Met Glu Ala Val Glu Arg Asn Val Gly Val Ile Val Ala Ala Val
        230                 235                 240

ctt gta acc ctg att ctc ctg gga atc ttg gtt ttt ggc atc tgg ttt     1063
Leu Val Thr Leu Ile Leu Leu Gly Ile Leu Val Phe Gly Ile Trp Phe
    245                 250                 255

gcc tat agc cga ggc cac ttt gac aga aca aag aaa ggg act tcg agt     1111
Ala Tyr Ser Arg Gly His Phe Asp Arg Thr Lys Lys Gly Thr Ser Ser
260                 265                 270                 275

aag aag gtg att tac agc cag cct agt gcc cga agt gaa gga gaa ttc     1159
Lys Lys Val Ile Tyr Ser Gln Pro Ser Ala Arg Ser Glu Gly Glu Phe
                280                 285                 290

aaa cag acc tcg tca ttc ctg gtg tgagcctggt cggctcaccg cctatcatct    1213
Lys Gln Thr Ser Ser Phe Leu Val
            295

gcatttgcct tactcaggtg ctactggact ctggcccctg atgtctgtag tttcacagga   1273

tgccttattt gtcttctaca ccccacaggg ccccctactt cttcggatgt gtttttaata   1333

atgtcagcta tgtgccccat cctccttcat gccctccctc cctttcctac cactgctgag   1393

tggcctggaa cttgtttaaa gtgtttattc cccatttctt tgagggatca ggaaggaatc   1453

ctgggtatgc cattgacttc ccttctaagt agacagcaaa aatggcgggg gtcgcaggaa   1513

tctgcactca actgcccacc tggctggcag ggatctttga ataggtatct tgagcttggt   1573

tctgggctct ttccttgtgt actgacgacc agggccagct gttctagagt gggaattaga   1633

ggctagagcg gctgaaatgg ttgtttggtg atgacactgg ggtccttcca tctctggggc   1693
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ccactctctt ctgtcttccc atgggaagtg ccactgggat ccctctgccc tgtcctcctg 1753

aatacaagct gactgacatt gactgtgtct gtggaaaatg ggagctcttg ttgtggagag 1813

catagtaaat tttcagagaa cttgaagcga aaaggattta aaaccgctgc tctaaagaaa 1873

agaaaactgg aggctgggcg cagtggctca cgcctgtaat cccagaggct gaggcaggcg 1933

gatcacctga ggtcgggagt tcgggatcag cctgaccaac atggagaaac cctgctggaa 1993

atacagagtt agccaggcat ggtggtgcat gcctgtagtc ccagctgctc aggagcctgg 2053

caacaagagc aaaactccag ctcaaaaaaa aaaaaaaaaa aaaaaaa 2100

<210> 54

<211> 299

<212> PRT

<213> AF111713 JAM1, junctional adhesion molecule 1

<400> 54

Met Gly Thr Lys Ala Gln Val Glu Arg Lys Leu Leu Cys Leu Phe Ile
1   5   10   15

Leu Ala Ile Leu Leu Cys Ser Leu Ala Leu Gly Ser Val Thr Val His
            20   25   30

Ser Ser Glu Pro Glu Val Arg Ile Pro Glu Asn Asn Pro Val Lys Leu
        35   40   45

Ser Cys Ala Tyr Ser Gly Phe Ser Ser Pro Arg Val Glu Trp Lys Phe
    50   55   60

Asp Gln Gly Asp Thr Thr Arg Leu Val Cys Tyr Asn Asn Lys Ile Thr
65   70   75   80

Ala Ser Tyr Glu Asp Arg Val Thr Phe Leu Pro Thr Gly Ile Thr Phe
                85   90   95

Lys Ser Val Thr Arg Glu Asp Thr Gly Thr Tyr Thr Cys Met Val Ser
            100   105   110

Glu Glu Gly Gly Asn Ser Tyr Gly Glu Val Lys Val Lys Leu Ile Val
        115   120   125

Leu Val Pro Pro Ser Lys Pro Thr Val Asn Ile Pro Ser Ser Ala Thr
    130   135   140

Ile Gly Asn Arg Ala Val Leu Thr Cys Ser Glu Gln Asp Gly Ser Pro
145   150   155   160

Pro Ser Glu Tyr Thr Trp Phe Lys Asp Gly Ile Val Met Pro Thr Asn
165 170 175

Pro Lys Ser Thr Arg Ala Phe Ser Asn Ser Ser Tyr Val Leu Asn Pro
180 185 190

Thr Thr Gly Glu Leu Val Phe Asp Pro Leu Ser Ala Ser Asp Thr Gly
195 200 205

Glu Tyr Ser Cys Glu Ala Arg Asn Gly Tyr Gly Thr Pro Met Thr Ser
210 215 220

Asn Ala Val Arg Met Glu Ala Val Glu Arg Asn Val Gly Val Ile Val
225 230 235 240

Ala Ala Val Leu Val Thr Leu Ile Leu Leu Gly Ile Leu Val Phe Gly
245 250 255

Ile Trp Phe Ala Tyr Ser Arg Gly His Phe Asp Arg Thr Lys Lys Gly
260 265 270

Thr Ser Ser Lys Lys Val Ile Tyr Ser Gln Pro Ser Ala Arg Ser Glu
275 280 285

Gly Glu Phe Lys Gln Thr Ser Ser Phe Leu Val
290 295

<210> 55

<211> 2154

<212> DNA

<213> NM_006636 MTHFD2, methylene tetrahydrofolate

<220>

<221> CDS

<222> (77)..(1108)

<223>

<400> 55
atataaccgc gtggcccgcg cgcgcgcttc cctcccggcg cagtcaccgg cgcggtctat 60

ggctgcgact tctcta atg tct gct ttg gct gcc cgg ctg ctg cag ccc gcg 112
Met Ser Ala Leu Ala Ala Arg Leu Leu Gln Pro Ala
1 5 10

cac agc tgc tcc ctt cgc ctt cgc cct ttc cac ctc gcg gca gtt cga 160
His Ser Cys Ser Leu Arg Leu Arg Pro Phe His Leu Ala Ala Val Arg
15 20 25

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aat gaa gct gtt gtc att tct gga agg aaa ctg gcc cag cag atc aag         208
Asn Glu Ala Val Val Ile Ser Gly Arg Lys Leu Ala Gln Gln Ile Lys
    30                  35                  40

cag gaa gtg cgg cag gag gta gaa gag tgg gtg gcc tca ggc aac aaa         256
Gln Glu Val Arg Gln Glu Val Glu Glu Trp Val Ala Ser Gly Asn Lys
45                  50                  55                  60

cgg cca cac ctg agt gtg atc ctg gtt ggc gag aat cct gca agt cac         304
Arg Pro His Leu Ser Val Ile Leu Val Gly Glu Asn Pro Ala Ser His
                65                  70                  75

tcc tat gtc ctc aac aaa acc agg gca gct gca gtt gtg gga atc aac         352
Ser Tyr Val Leu Asn Lys Thr Arg Ala Ala Ala Val Val Gly Ile Asn
            80                  85                  90

agt gag aca att atg aaa cca gct tca att tca gag gaa gaa ttg ttg         400
Ser Glu Thr Ile Met Lys Pro Ala Ser Ile Ser Glu Glu Glu Leu Leu
        95                  100                 105

aat tta atc aat aaa ctg aat aat gat gat aat gta gat ggc ctc ctt         448
Asn Leu Ile Asn Lys Leu Asn Asn Asp Asp Asn Val Asp Gly Leu Leu
    110                 115                 120

gtt cag ttg cct ctt cca gag cat att gat gag aga agg atc tgc aat         496
Val Gln Leu Pro Leu Pro Glu His Ile Asp Glu Arg Arg Ile Cys Asn
125                 130                 135                 140

gct gtt tct cca gac aag gat gtt gat ggc ttt cat gta att aat gta         544
Ala Val Ser Pro Asp Lys Asp Val Asp Gly Phe His Val Ile Asn Val
                145                 150                 155

gga cga atg tgt ttg gat cag tat tcc atg tta ccg gct act cca tgg         592
Gly Arg Met Cys Leu Asp Gln Tyr Ser Met Leu Pro Ala Thr Pro Trp
            160                 165                 170

ggt gtg tgg gaa ata atc aag cga act ggc att cca acc cta ggg aag         640
Gly Val Trp Glu Ile Ile Lys Arg Thr Gly Ile Pro Thr Leu Gly Lys
        175                 180                 185

aat gtg gtt gtg gct gga agg tca aaa aac gtt gga atg ccc att gca         688
Asn Val Val Val Ala Gly Arg Ser Lys Asn Val Gly Met Pro Ile Ala
    190                 195                 200

atg tta ctg cac aca gat ggg gcg cat gaa cgt ccc gga ggt gat gcc         736
Met Leu Leu His Thr Asp Gly Ala His Glu Arg Pro Gly Gly Asp Ala
205                 210                 215                 220

act gtt aca ata tct cat cga tat act ccc aaa gag cag ttg aag aaa         784
Thr Val Thr Ile Ser His Arg Tyr Thr Pro Lys Glu Gln Leu Lys Lys
                225                 230                 235

cat aca att ctt gca gat att gta ata tct gct gca ggt att cca aat         832
His Thr Ile Leu Ala Asp Ile Val Ile Ser Ala Ala Gly Ile Pro Asn
            240                 245                 250

ctg atc aca gca gat atg atc aag gaa gga gca gca gtc att gat gtg         880
Leu Ile Thr Ala Asp Met Ile Lys Glu Gly Ala Ala Val Ile Asp Val
        255                 260                 265

gga ata aat aga gtt cac gat cct gta act gcc aaa ccc aag ttg gtt         928
Gly Ile Asn Arg Val His Asp Pro Val Thr Ala Lys Pro Lys Leu Val
    270                 275                 280

gga gat gtg gat ttt gaa gga gtc aga caa aaa gct ggg tat atc act         976
Gly Asp Val Asp Phe Glu Gly Val Arg Gln Lys Ala Gly Tyr Ile Thr
285                 290                 295                 300
```

```
cca gtt cct gga ggt gtt ggc ccc atg aca gtg gca atg cta atg aag      1024
Pro Val Pro Gly Gly Val Gly Pro Met Thr Val Ala Met Leu Met Lys
                305                 310                 315

aat acc att att gct gca aaa aag gtg ctg agg ctt gaa gag cga gaa      1072
Asn Thr Ile Ile Ala Ala Lys Lys Val Leu Arg Leu Glu Glu Arg Glu
            320                 325                 330

gtg ctg aag tct aaa gag ctt ggg gta gcc act aat taactactgt           1118
Val Leu Lys Ser Lys Glu Leu Gly Val Ala Thr Asn
        335                 340

gtcttctgtg tcacaaacag cactccaggc cagctcaaga agcaaagcag gccaatagaa    1178

atgcaatatt tttaatttat tctactgaaa tggtttaaaa tgatgccttg tatttattga    1238

aagcttaaat gggtgggtgt ttctgcacat acctctgcag tacctcacca gggagcattc    1298

cagtatcatg cagggtcctg tgatctagcc aggagcagcc attaacctag tgattaatat    1358

gggagacatt accatatgga ggatggatgc ttcactttgt caagcacctc agttacacat    1418

tcgccttttc taggattgca tttcccaagt gctattgcaa taacagttga tactcatttt    1478

aggtaccaga ccttttgagt tcaactgatc aaaccaaagg aaaagtgttg ctagagaaaa    1538

ttggggaaaa ggtgaaaaag aaaaaatggt agtaattgag cagaaaaaaa ttaatttata    1598

tatgtattga ttggcaacca gatttatcta agtagaactg aattggctag gaaaaaagaa    1658

aaactgcatg ttaatcattt tcctaagctg tccttttgag gcttagtcag tttattggga    1718

aaatgtttag gattattcct tgctattagt actcatttta tgtatgttac ccttcagtaa    1778

gttctcccca ttttagtttt ctaggactga aaggattctt ttctacatta tacatgtgtg    1838

ttgtcatatt tggcttttgc tatatacttt aacttcattg ttaaattttt gtattgtata    1898

gtttctttgg tgtatcttaa aacctatttt tgaaaaacaa acttggcttg ataatcattt    1958

gggcagcttg ggtaagtacg caacttactt ttccaccaaa gaactgtcag cagctgcctg    2018

cttttctgtg atgtatgtat cctgttgact tttccagaaa ttttttaaga gtttgagtta    2078

ctattgaatt taatcagact ttctgattaa agggttttct ttcttttttta ataaaacaca    2138

tctgtctggt atggta                                                    2154
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<210> 56

<211> 344

<212> PRT

<213> NM_006636 MTHFD2, methylene tetrahydrofolate

<400> 56

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Met Ser Ala Leu Ala Ala Arg Leu Leu Gln Pro Ala His Ser Cys Ser
1               5                   10                  15

Leu Arg Leu Arg Pro Phe His Leu Ala Ala Val Arg Asn Glu Ala Val
            20                  25                  30
```

```
Val Ile Ser Gly Arg Lys Leu Ala Gln Gln Ile Lys Gln Glu Val Arg
        35                  40                  45

Gln Glu Val Glu Glu Trp Val Ala Ser Gly Asn Lys Arg Pro His Leu
    50                  55                  60

Ser Val Ile Leu Val Gly Glu Asn Pro Ala Ser His Ser Tyr Val Leu
65                  70                  75                  80

Asn Lys Thr Arg Ala Ala Ala Val Val Gly Ile Asn Ser Glu Thr Ile
                85                  90                  95

Met Lys Pro Ala Ser Ile Ser Glu Glu Glu Leu Leu Asn Leu Ile Asn
            100                 105                 110

Lys Leu Asn Asn Asp Asp Asn Val Asp Gly Leu Leu Val Gln Leu Pro
        115                 120                 125

Leu Pro Glu His Ile Asp Glu Arg Arg Ile Cys Asn Ala Val Ser Pro
    130                 135                 140

Asp Lys Asp Val Asp Gly Phe His Val Ile Asn Val Gly Arg Met Cys
145                 150                 155                 160

Leu Asp Gln Tyr Ser Met Leu Pro Ala Thr Pro Trp Gly Val Trp Glu
                165                 170                 175

Ile Ile Lys Arg Thr Gly Ile Pro Thr Leu Gly Lys Asn Val Val Val
            180                 185                 190

Ala Gly Arg Ser Lys Asn Val Gly Met Pro Ile Ala Met Leu Leu His
        195                 200                 205

Thr Asp Gly Ala His Glu Arg Pro Gly Gly Asp Ala Thr Val Thr Ile
    210                 215                 220

Ser His Arg Tyr Thr Pro Lys Glu Gln Leu Lys Lys His Thr Ile Leu
225                 230                 235                 240

Ala Asp Ile Val Ile Ser Ala Ala Gly Ile Pro Asn Leu Ile Thr Ala
                245                 250                 255

Asp Met Ile Lys Glu Gly Ala Ala Val Ile Asp Val Gly Ile Asn Arg
            260                 265                 270

Val His Asp Pro Val Thr Ala Lys Pro Lys Leu Val Gly Asp Val Asp
        275                 280                 285

Phe Glu Gly Val Arg Gln Lys Ala Gly Tyr Ile Thr Pro Val Pro Gly
    290                 295                 300
```

```
Gly Val Gly Pro Met Thr Val Ala Met Leu Met Lys Asn Thr Ile Ile
305                 310                 315                 320

Ala Ala Lys Lys Val Leu Arg Leu Glu Glu Arg Glu Val Leu Lys Ser
                325                 330                 335

Lys Glu Leu Gly Val Ala Thr Asn
            340
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<210> 57

<211> 1117

<212> DNA

<213> NM_006149 galectin 4, LGALS4

<220>

<221> CDS

<222> (57)..(1025)

<223>

<400> 57

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                                                              Met
                                                              1

gcc tat gtc ccc gca ccg ggc tac cag ccc acc tac aac ccg acg ctg       107
Ala Tyr Val Pro Ala Pro Gly Tyr Gln Pro Thr Tyr Asn Pro Thr Leu
            5                   10                  15

cct tac tac cag ccc atc ccg ggc ggg ctc aac gtg gga atg tct gtt       155
Pro Tyr Tyr Gln Pro Ile Pro Gly Gly Leu Asn Val Gly Met Ser Val
        20                  25                  30

tac atc caa gga gtg gcc agc gag cac atg aag cgg ttc ttc gtg aac       203
Tyr Ile Gln Gly Val Ala Ser Glu His Met Lys Arg Phe Phe Val Asn
    35                  40                  45

ttt gtg gtt ggg cag gat ccg ggc tca gac gtc gcc ttc cac ttc aat       251
Phe Val Val Gly Gln Asp Pro Gly Ser Asp Val Ala Phe His Phe Asn
50                  55                  60                  65

ccg cgg ttt gac ggc tgg gac aag gtg gtc ttc aac acg ttg cag ggc       299
Pro Arg Phe Asp Gly Trp Asp Lys Val Val Phe Asn Thr Leu Gln Gly
                70                  75                  80

ggg aag tgg ggc agc gag gag agg aag agg agc atg ccc ttc aaa aag       347
Gly Lys Trp Gly Ser Glu Glu Arg Lys Arg Ser Met Pro Phe Lys Lys
            85                  90                  95

ggt gcc gcc ttt gag ctg gtc ttc ata gtc ctg gct gag cac tac aag       395
Gly Ala Ala Phe Glu Leu Val Phe Ile Val Leu Ala Glu His Tyr Lys
        100                 105                 110

gtg gtg gta aat gga aat ccc ttc tat gag tac ggg cac cgg ctt ccc       443
Val Val Val Asn Gly Asn Pro Phe Tyr Glu Tyr Gly His Arg Leu Pro
```

115 120 125

cta cag atg gtc acc cac ctg caa gtg gat ggg gat ctg caa ctt caa 491
Leu Gln Met Val Thr His Leu Gln Val Asp Gly Asp Leu Gln Leu Gln
130 135 140 145

tca atc aac ttc atc gga ggc cag ccc ctc cgg ccc cag gga ccc ccg 539
Ser Ile Asn Phe Ile Gly Gly Gln Pro Leu Arg Pro Gln Gly Pro Pro
150 155 160

atg atg cca cct tac cct ggt ccc gga cat tgc cat caa cag ctg aac 587
Met Met Pro Pro Tyr Pro Gly Pro Gly His Cys His Gln Gln Leu Asn
165 170 175

agc ctg ccc acc atg gaa gga ccc cca acc ttc aac ccg cct gtg cca 635
Ser Leu Pro Thr Met Glu Gly Pro Pro Thr Phe Asn Pro Pro Val Pro
180 185 190

tat ttc ggg agg ctg caa gga ggg ctc aca gct cga aga acc atc atc 683
Tyr Phe Gly Arg Leu Gln Gly Gly Leu Thr Ala Arg Arg Thr Ile Ile
195 200 205

atc aag ggc tat gtg cct ccc aca ggc aag agc ttt gct atc aac ttc 731
Ile Lys Gly Tyr Val Pro Pro Thr Gly Lys Ser Phe Ala Ile Asn Phe
210 215 220 225

aag gtg ggc tcc tca ggg gac ata gct ctg cac att aat ccc cgc atg 779
Lys Val Gly Ser Ser Gly Asp Ile Ala Leu His Ile Asn Pro Arg Met
230 235 240

ggc aac ggt acc gtg gtc cgg aac agc ctt ctg aat ggc tcg tgg gga 827
Gly Asn Gly Thr Val Val Arg Asn Ser Leu Leu Asn Gly Ser Trp Gly
245 250 255

tcc gag gag aag aag atc acc cac aac cca ttt ggt ccc gga cag ttc 875
Ser Glu Glu Lys Lys Ile Thr His Asn Pro Phe Gly Pro Gly Gln Phe
260 265 270

ttt gat ctg tcc att cgc tgt ggc ttg gat cgc ttc aag gtt tac gcc 923
Phe Asp Leu Ser Ile Arg Cys Gly Leu Asp Arg Phe Lys Val Tyr Ala
275 280 285

aat ggc cag cac ctc ttt gac ttt gcc cat cgc ctc tcg gcc ttc cag 971
Asn Gly Gln His Leu Phe Asp Phe Ala His Arg Leu Ser Ala Phe Gln
290 295 300 305

agg gtg gac aca ttg gaa atc cag ggt gat gtc acc ttg tcc tat gtc 1019
Arg Val Asp Thr Leu Glu Ile Gln Gly Asp Val Thr Leu Ser Tyr Val
310 315 320

cag atc taatctattc ctggggccat aactcatggg aaaacagaat tatcccctag 1075
Gln Ile

gactcctttc taagccccta ataaaatgtc tgagggtgtc tc 1117

<210> 58

<211> 323

<212> PRT

<213> NM_006149 galectin 4, LGALS4

<400> 58

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Met Ala Tyr Val Pro Ala Pro Gly Tyr Gln Pro Thr Tyr Asn Pro Thr
1               5                   10                  15

Leu Pro Tyr Tyr Gln Pro Ile Pro Gly Gly Leu Asn Val Gly Met Ser
            20                  25                  30

Val Tyr Ile Gln Gly Val Ala Ser Glu His Met Lys Arg Phe Phe Val
        35                  40                  45

Asn Phe Val Val Gly Gln Asp Pro Gly Ser Asp Val Ala Phe His Phe
    50                  55                  60

Asn Pro Arg Phe Asp Gly Trp Asp Lys Val Val Phe Asn Thr Leu Gln
65                  70                  75                  80

Gly Gly Lys Trp Gly Ser Glu Glu Arg Lys Arg Ser Met Pro Phe Lys
                85                  90                  95

Lys Gly Ala Ala Phe Glu Leu Val Phe Ile Val Leu Ala Glu His Tyr
            100                 105                 110

Lys Val Val Val Asn Gly Asn Pro Phe Tyr Glu Tyr Gly His Arg Leu
        115                 120                 125

Pro Leu Gln Met Val Thr His Leu Gln Val Asp Gly Asp Leu Gln Leu
    130                 135                 140

Gln Ser Ile Asn Phe Ile Gly Gly Gln Pro Leu Arg Pro Gln Gly Pro
145                 150                 155                 160

Pro Met Met Pro Pro Tyr Pro Gly Pro Gly His Cys His Gln Gln Leu
                165                 170                 175

Asn Ser Leu Pro Thr Met Glu Gly Pro Pro Thr Phe Asn Pro Pro Val
            180                 185                 190

Pro Tyr Phe Gly Arg Leu Gln Gly Gly Leu Thr Ala Arg Arg Thr Ile
        195                 200                 205

Ile Ile Lys Gly Tyr Val Pro Pro Thr Gly Lys Ser Phe Ala Ile Asn
    210                 215                 220

Phe Lys Val Gly Ser Ser Gly Asp Ile Ala Leu His Ile Asn Pro Arg
225                 230                 235                 240

Met Gly Asn Gly Thr Val Val Arg Asn Ser Leu Leu Asn Gly Ser Trp
                245                 250                 255

Gly Ser Glu Glu Lys Lys Ile Thr His Asn Pro Phe Gly Pro Gly Gln
            260                 265                 270
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Phe Phe Asp Leu Ser Ile Arg Cys Gly Leu Asp Arg Phe Lys Val Tyr
        275                 280                 285

Ala Asn Gly Gln His Leu Phe Asp Phe Ala His Arg Leu Ser Ala Phe
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Val Gln Ile


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atg ata ctt cag gcc cat ctt cac tcc ctg tgt ctt ctt atg ctt tat       168
Met Ile Leu Gln Ala His Leu His Ser Leu Cys Leu Leu Met Leu Tyr
1               5                   10                  15

ttg gca act gga tat ggc caa gag ggg aag ttt agt gga ccc ctg aaa       216
Leu Ala Thr Gly Tyr Gly Gln Glu Gly Lys Phe Ser Gly Pro Leu Lys
            20                  25                  30

ccc atg aca ttt tct att tat gaa ggc caa gaa ccg agt caa att ata       264
Pro Met Thr Phe Ser Ile Tyr Glu Gly Gln Glu Pro Ser Gln Ile Ile
        35                  40                  45

ttc cag ttt aag gcc aat cct cct gct gtg act ttt gaa cta act ggg       312
Phe Gln Phe Lys Ala Asn Pro Pro Ala Val Thr Phe Glu Leu Thr Gly
    50                  55                  60

gag aca gac aac ata ttt gtg ata gaa cgg gag gga ctt ctg tat tac       360
Glu Thr Asp Asn Ile Phe Val Ile Glu Arg Glu Gly Leu Leu Tyr Tyr
65                  70                  75                  80

aac aga gcc ttg gac agg gaa aca aga tct act cac aat ctc cag gtt       408
Asn Arg Ala Leu Asp Arg Glu Thr Arg Ser Thr His Asn Leu Gln Val
                85                  90                  95

gca gcc ctg gac gct aat gga att ata gtg gag ggt cca gtc cct atc       456
Ala Ala Leu Asp Ala Asn Gly Ile Ile Val Glu Gly Pro Val Pro Ile
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            100                 105                 110

acc ata gaa gtg aag gac atc aac gac aat cga ccc acg ttt ctc cag        504
Thr Ile Glu Val Lys Asp Ile Asn Asp Asn Arg Pro Thr Phe Leu Gln
        115                 120                 125

tca aag tac gaa ggc tca gta agg cag aac tct cgc cca gga aag ccc        552
Ser Lys Tyr Glu Gly Ser Val Arg Gln Asn Ser Arg Pro Gly Lys Pro
    130                 135                 140

ttc ttg tat gtc aat gcc aca gac ctg gat gat ccg gcc act ccc aat        600
Phe Leu Tyr Val Asn Ala Thr Asp Leu Asp Asp Pro Ala Thr Pro Asn
145                 150                 155                 160

ggc cag ctt tat tac cag att gtc atc cag ctt ccc atg atc aac aat        648
Gly Gln Leu Tyr Tyr Gln Ile Val Ile Gln Leu Pro Met Ile Asn Asn
                165                 170                 175

gtc atg tac ttt cag atc aac aac aaa acg gga gcc atc tct ctt acc        696
Val Met Tyr Phe Gln Ile Asn Asn Lys Thr Gly Ala Ile Ser Leu Thr
            180                 185                 190

cga gag gga tct cag gaa ttg aat cct gct aag aat cct tcc tat aat        744
Arg Glu Gly Ser Gln Glu Leu Asn Pro Ala Lys Asn Pro Ser Tyr Asn
        195                 200                 205

ctg gtg atc tca gtg aag gac atg gga ggc cag agt gag aat tcc ttc        792
Leu Val Ile Ser Val Lys Asp Met Gly Gly Gln Ser Glu Asn Ser Phe
    210                 215                 220

agt gat acc aca tct gtg gat atc ata gtg aca gag aat att tgg aaa        840
Ser Asp Thr Thr Ser Val Asp Ile Ile Val Thr Glu Asn Ile Trp Lys
225                 230                 235                 240

gca cca aaa cct gtg gag atg gtg gaa aac tca act gat cct cac ccc        888
Ala Pro Lys Pro Val Glu Met Val Glu Asn Ser Thr Asp Pro His Pro
                245                 250                 255

atc aaa atc act cag gtg cgg tgg aat gat ccc ggt gca caa tat tcc        936
Ile Lys Ile Thr Gln Val Arg Trp Asn Asp Pro Gly Ala Gln Tyr Ser
            260                 265                 270

tta gtt gac aaa gag aag ctg cca aga ttc cca ttt tca att gac cag        984
Leu Val Asp Lys Glu Lys Leu Pro Arg Phe Pro Phe Ser Ile Asp Gln
        275                 280                 285

gaa gga gat att tac gtg act cag ccc ttg gac cga gaa gaa aag gat       1032
Glu Gly Asp Ile Tyr Val Thr Gln Pro Leu Asp Arg Glu Glu Lys Asp
    290                 295                 300

gca tat gtt ttt tat gca gtt gca aag gat gag tac gga aaa cca ctt       1080
Ala Tyr Val Phe Tyr Ala Val Ala Lys Asp Glu Tyr Gly Lys Pro Leu
305                 310                 315                 320

tca tat ccg ctg gaa att cat gta aaa gtt aaa gat att aat gat aat       1128
Ser Tyr Pro Leu Glu Ile His Val Lys Val Lys Asp Ile Asn Asp Asn
                325                 330                 335

cca cct aca tgt ccg tca cca gta acc gta ttt gag gtc cag gag aat       1176
Pro Pro Thr Cys Pro Ser Pro Val Thr Val Phe Glu Val Gln Glu Asn
            340                 345                 350

gaa cga ctg ggt aac agt atc ggg acc ctt act gca cat gac agg gat       1224
Glu Arg Leu Gly Asn Ser Ile Gly Thr Leu Thr Ala His Asp Arg Asp
        355                 360                 365

gaa gaa aat act gcc aac agt ttt cta aac tac agg att gtg gag caa       1272
Glu Glu Asn Thr Ala Asn Ser Phe Leu Asn Tyr Arg Ile Val Glu Gln
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370 375 380

act ccc aaa ctt ccc atg gat gga ctc ttc cta atc caa acc tat gct 1320
Thr Pro Lys Leu Pro Met Asp Gly Leu Phe Leu Ile Gln Thr Tyr Ala
385 390 395 400

gga atg tta cag tta gct aaa cag tcc ttg aag aag caa gat act cct 1368
Gly Met Leu Gln Leu Ala Lys Gln Ser Leu Lys Lys Gln Asp Thr Pro
405 410 415

cag tac aac tta acg ata gag gtg tct gac aaa gat ttc aag acc ctt 1416
Gln Tyr Asn Leu Thr Ile Glu Val Ser Asp Lys Asp Phe Lys Thr Leu
420 425 430

tgt ttt gtg caa atc aac gtt att gat atc aat gat cag atc ccc atc 1464
Cys Phe Val Gln Ile Asn Val Ile Asp Ile Asn Asp Gln Ile Pro Ile
435 440 445

ttt gaa aaa tca gat tat gga aac ctg act ctt gct gaa gac aca aac 1512
Phe Glu Lys Ser Asp Tyr Gly Asn Leu Thr Leu Ala Glu Asp Thr Asn
450 455 460

att ggg tcc acc atc tta acc atc cag gcc act gat gct gat gag cca 1560
Ile Gly Ser Thr Ile Leu Thr Ile Gln Ala Thr Asp Ala Asp Glu Pro
465 470 475 480

ttt act ggg agt tct aaa att ctg tat cat atc ata aag gga gac agt 1608
Phe Thr Gly Ser Ser Lys Ile Leu Tyr His Ile Ile Lys Gly Asp Ser
485 490 495

gag gga cgc ctg ggg gtt gac aca gat ccc cat acc aac acc gga tat 1656
Glu Gly Arg Leu Gly Val Asp Thr Asp Pro His Thr Asn Thr Gly Tyr
500 505 510

gtc ata att aaa aag cct ctt gat ttt gaa aca gca gct gtt tcc aac 1704
Val Ile Ile Lys Lys Pro Leu Asp Phe Glu Thr Ala Ala Val Ser Asn
515 520 525

att gtg ttc aaa gca gaa aat cct gag cct cta gtg ttt ggt gtg aag 1752
Ile Val Phe Lys Ala Glu Asn Pro Glu Pro Leu Val Phe Gly Val Lys
530 535 540

tac aat gca agt tct ttt gcc aag ttc acg ctt att gtg aca gat gtg 1800
Tyr Asn Ala Ser Ser Phe Ala Lys Phe Thr Leu Ile Val Thr Asp Val
545 550 555 560

aat gaa gca cct caa ttt tcc caa cac gta ttc caa gcg aaa gtc agt 1848
Asn Glu Ala Pro Gln Phe Ser Gln His Val Phe Gln Ala Lys Val Ser
565 570 575

gag gat gta gct ata ggc act aaa gtg ggc aat gtg act gcc aag gat 1896
Glu Asp Val Ala Ile Gly Thr Lys Val Gly Asn Val Thr Ala Lys Asp
580 585 590

cca gaa ggt ctg gac ata agc tat tca ctg agg gga gac aca aga ggt 1944
Pro Glu Gly Leu Asp Ile Ser Tyr Ser Leu Arg Gly Asp Thr Arg Gly
595 600 605

tgg ctt aaa att gac cac gtg act ggt gag atc ttt agt gtg gct cca 1992
Trp Leu Lys Ile Asp His Val Thr Gly Glu Ile Phe Ser Val Ala Pro
610 615 620

ttg gac aga gaa gcc gga agt cca tat cgg gta caa gtg gtg gcc aca 2040
Leu Asp Arg Glu Ala Gly Ser Pro Tyr Arg Val Gln Val Val Ala Thr
625 630 635 640

gaa gta ggg ggg tct tcc ttg agc tct gtg tca gag ttc cac ctg atc 2088
Glu Val Gly Gly Ser Ser Leu Ser Ser Val Ser Glu Phe His Leu Ile

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                645                 650                 655

ctt atg gat gtg aat gac aac cct ccc agg cta gcc aag gac tac acg        2136
Leu Met Asp Val Asn Asp Asn Pro Pro Arg Leu Ala Lys Asp Tyr Thr
            660                 665                 670

ggc ttg ttc ttc tgc cat ccc ctc agt gca cct gga agt ctc att ttc        2184
Gly Leu Phe Phe Cys His Pro Leu Ser Ala Pro Gly Ser Leu Ile Phe
        675                 680                 685

gag gct act gat gat gat cag cac tta ttt cgg ggt ccc cat ttt aca        2232
Glu Ala Thr Asp Asp Asp Gln His Leu Phe Arg Gly Pro His Phe Thr
    690                 695                 700

ttt tcc ctc ggc agt gga agc tta caa aac gac tgg gaa gtt tcc aaa        2280
Phe Ser Leu Gly Ser Gly Ser Leu Gln Asn Asp Trp Glu Val Ser Lys
705                 710                 715                 720

atc aat ggt act cat gcc cga ctg tct acc agg cac aca gag ttt gag        2328
Ile Asn Gly Thr His Ala Arg Leu Ser Thr Arg His Thr Glu Phe Glu
                725                 730                 735

gag agg gag tat gtc gtc ttg atc cgc atc aat gat ggg ggt cgg cca        2376
Glu Arg Glu Tyr Val Val Leu Ile Arg Ile Asn Asp Gly Gly Arg Pro
            740                 745                 750

ccc ttg gaa ggc att gtt tct tta cca gtt aca ttc tgc agt tgt gtg        2424
Pro Leu Glu Gly Ile Val Ser Leu Pro Val Thr Phe Cys Ser Cys Val
        755                 760                 765

gaa gga agt tgt ttc cgg cca gca ggt cac cag act ggg ata ccc act        2472
Glu Gly Ser Cys Phe Arg Pro Ala Gly His Gln Thr Gly Ile Pro Thr
    770                 775                 780

gtg ggc atg gca gtt ggt ata ctg ctg acc acc ctt ctg gtg att ggt        2520
Val Gly Met Ala Val Gly Ile Leu Leu Thr Thr Leu Leu Val Ile Gly
785                 790                 795                 800

ata att tta gca gtt gtg ttt atc cgc ata aag aag gat aaa ggc aaa        2568
Ile Ile Leu Ala Val Val Phe Ile Arg Ile Lys Lys Asp Lys Gly Lys
                805                 810                 815

gat aat gtt gaa agt gct caa gca tct gaa gtc aaa cct ctg aga agc        2616
Asp Asn Val Glu Ser Ala Gln Ala Ser Glu Val Lys Pro Leu Arg Ser
            820                 825                 830

tgaatttgaa aaggaatgtt tgaatttata tagcaagtgc tatttcagca acaaccatct     2676

catcctatta cttttcatct aacgtgcatt ataatttttt aaacagatat tccctcttgt     2736

cctttaatat ttgctaaata tttctttttt gaggtggagt cttgctctgt cgcccaggct     2796

ggagtacagt ggtgtgatcc cagctcactg caacctccgc ctcctgggtt cacatgattc     2856

tcctgcctca gcttcctaag tagctgggtt tacaggcacc caccaccatg cccagctaat     2916

ttttgtattt ttaatagaga cggggtttcg ccatttggcc aggctggtct tgaactcctg     2976

acgtcaagtg atctgcctgc cttggtctcc caatacaggc atgaaccact gcacccacct     3036

acttagatat ttcatgtgct atagacatta gagagatttt tcatttttcc atgacatttt     3096

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taaatattct gtacattttt tctttatcaa ggagatatat cagtgttgtc tcatagaact     3216

gcctggattc catttatgtt ttttctgatt ccatcctgtg tccccttcat ccttgactcc     3276
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ttaaccatct ttaatcaatg tgacatgttg ctctttggct gaaattcttc aacttggaaa 3456

tgacacagac ccacagaagg tgttcaaaca caacctactc tgcaaacctt ggtaaaggaa 3516

ccagtcagct ggccagattt cctcactacc tgccatgcat acatgctgcg catgttttct 3576

tcattcgtat gttagtaaag ttttggttat tatatattta acatgtggaa gaaaacaaga 3636

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Pro Met Thr Phe Ser Ile Tyr Glu Gly Gln Glu Pro Ser Gln Ile Ile
35 40 45

Phe Gln Phe Lys Ala Asn Pro Pro Ala Val Thr Phe Glu Leu Thr Gly
50 55 60

Glu Thr Asp Asn Ile Phe Val Ile Glu Arg Glu Gly Leu Leu Tyr Tyr
65 70 75 80

Asn Arg Ala Leu Asp Arg Glu Thr Arg Ser Thr His Asn Leu Gln Val
85 90 95

Ala Ala Leu Asp Ala Asn Gly Ile Ile Val Glu Gly Pro Val Pro Ile
100 105 110

Thr Ile Glu Val Lys Asp Ile Asn Asp Asn Arg Pro Thr Phe Leu Gln
115 120 125

Ser Lys Tyr Glu Gly Ser Val Arg Gln Asn Ser Arg Pro Gly Lys Pro
130 135 140

Phe Leu Tyr Val Asn Ala Thr Asp Leu Asp Asp Pro Ala Thr Pro Asn
145 150 155 160

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Gly Gln Leu Tyr Tyr Gln Ile Val Ile Gln Leu Pro Met Ile Asn Asn
                165                 170                 175

Val Met Tyr Phe Gln Ile Asn Asn Lys Thr Gly Ala Ile Ser Leu Thr
            180                 185                 190

Arg Glu Gly Ser Gln Glu Leu Asn Pro Ala Lys Asn Pro Ser Tyr Asn
        195                 200                 205

Leu Val Ile Ser Val Lys Asp Met Gly Gly Gln Ser Glu Asn Ser Phe
    210                 215                 220

Ser Asp Thr Thr Ser Val Asp Ile Ile Val Thr Glu Asn Ile Trp Lys
225                 230                 235                 240

Ala Pro Lys Pro Val Glu Met Val Glu Asn Ser Thr Asp Pro His Pro
                245                 250                 255

Ile Lys Ile Thr Gln Val Arg Trp Asn Asp Pro Gly Ala Gln Tyr Ser
            260                 265                 270

Leu Val Asp Lys Glu Lys Leu Pro Arg Phe Pro Phe Ser Ile Asp Gln
        275                 280                 285

Glu Gly Asp Ile Tyr Val Thr Gln Pro Leu Asp Arg Glu Glu Lys Asp
    290                 295                 300

Ala Tyr Val Phe Tyr Ala Val Ala Lys Asp Glu Tyr Gly Lys Pro Leu
305                 310                 315                 320

Ser Tyr Pro Leu Glu Ile His Val Lys Val Lys Asp Ile Asn Asp Asn
                325                 330                 335

Pro Pro Thr Cys Pro Ser Pro Val Thr Val Phe Glu Val Gln Glu Asn
            340                 345                 350

Glu Arg Leu Gly Asn Ser Ile Gly Thr Leu Thr Ala His Asp Arg Asp
        355                 360                 365

Glu Glu Asn Thr Ala Asn Ser Phe Leu Asn Tyr Arg Ile Val Glu Gln
    370                 375                 380

Thr Pro Lys Leu Pro Met Asp Gly Leu Phe Leu Ile Gln Thr Tyr Ala
385                 390                 395                 400

Gly Met Leu Gln Leu Ala Lys Gln Ser Leu Lys Lys Gln Asp Thr Pro
                405                 410                 415

Gln Tyr Asn Leu Thr Ile Glu Val Ser Asp Lys Asp Phe Lys Thr Leu
            420                 425                 430
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Cys Phe Val Gln Ile Asn Val Ile Asp Ile Asn Asp Gln Ile Pro Ile
435 440 445

Phe Glu Lys Ser Asp Tyr Gly Asn Leu Thr Leu Ala Glu Asp Thr Asn
450 455 460

Ile Gly Ser Thr Ile Leu Thr Ile Gln Ala Thr Asp Ala Asp Glu Pro
465 470 475 480

Phe Thr Gly Ser Ser Lys Ile Leu Tyr His Ile Ile Lys Gly Asp Ser
485 490 495

Glu Gly Arg Leu Gly Val Asp Thr Asp Pro His Thr Asn Thr Gly Tyr
500 505 510

Val Ile Ile Lys Lys Pro Leu Asp Phe Glu Thr Ala Ala Val Ser Asn
515 520 525

Ile Val Phe Lys Ala Glu Asn Pro Glu Pro Leu Val Phe Gly Val Lys
530 535 540

Tyr Asn Ala Ser Ser Phe Ala Lys Phe Thr Leu Ile Val Thr Asp Val
545 550 555 560

Asn Glu Ala Pro Gln Phe Ser Gln His Val Phe Gln Ala Lys Val Ser
565 570 575

Glu Asp Val Ala Ile Gly Thr Lys Val Gly Asn Val Thr Ala Lys Asp
580 585 590

Pro Glu Gly Leu Asp Ile Ser Tyr Ser Leu Arg Gly Asp Thr Arg Gly
595 600 605

Trp Leu Lys Ile Asp His Val Thr Gly Glu Ile Phe Ser Val Ala Pro
610 615 620

Leu Asp Arg Glu Ala Gly Ser Pro Tyr Arg Val Gln Val Val Ala Thr
625 630 635 640

Glu Val Gly Gly Ser Ser Leu Ser Ser Val Ser Glu Phe His Leu Ile
645 650 655

Leu Met Asp Val Asn Asp Asn Pro Pro Arg Leu Ala Lys Asp Tyr Thr
660 665 670

Gly Leu Phe Phe Cys His Pro Leu Ser Ala Pro Gly Ser Leu Ile Phe
675 680 685

Glu Ala Thr Asp Asp Asp Gln His Leu Phe Arg Gly Pro His Phe Thr
690 695 700

Phe Ser Leu Gly Ser Gly Ser Leu Gln Asn Asp Trp Glu Val Ser Lys
705 710 715 720

Ile Asn Gly Thr His Ala Arg Leu Ser Thr Arg His Thr Glu Phe Glu
725 730 735

Glu Arg Glu Tyr Val Val Leu Ile Arg Ile Asn Asp Gly Gly Arg Pro
740 745 750

Pro Leu Glu Gly Ile Val Ser Leu Pro Val Thr Phe Cys Ser Cys Val
755 760 765

Glu Gly Ser Cys Phe Arg Pro Ala Gly His Gln Thr Gly Ile Pro Thr
770 775 780

Val Gly Met Ala Val Gly Ile Leu Leu Thr Thr Leu Leu Val Ile Gly
785 790 795 800

Ile Ile Leu Ala Val Val Phe Ile Arg Ile Lys Lys Asp Lys Gly Lys
805 810 815

Asp Asn Val Glu Ser Ala Gln Ala Ser Glu Val Lys Pro Leu Arg Ser
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ctt ttt gcc cac ata gca gct gta ccg att aag cat ctt cct gaa gaa 99
Leu Phe Ala His Ile Ala Ala Val Pro Ile Lys His Leu Pro Glu Glu
15 20 25 30

aat gta cat gat gca gat ttt ggt gaa cag aag gat att tca gaa atc 147
Asn Val His Asp Ala Asp Phe Gly Glu Gln Lys Asp Ile Ser Glu Ile
35 40 45

aat tta gct gca ggc ttg gac ctc ttt caa ggg gac atc ctc ttg cag 195
Asn Leu Ala Ala Gly Leu Asp Leu Phe Gln Gly Asp Ile Leu Leu Gln

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                50                  55                  60

aaa tcc aga aat ggc ctg aga gac cca aac acc agg tgg acg ttc ccc      243
Lys Ser Arg Asn Gly Leu Arg Asp Pro Asn Thr Arg Trp Thr Phe Pro
        65                  70                  75

att cct tac atc ttg gct gat aat ttg ggg ctg aat gct aaa gga gcc      291
Ile Pro Tyr Ile Leu Ala Asp Asn Leu Gly Leu Asn Ala Lys Gly Ala
    80                  85                  90

att ctg tat gcc ttt gag atg ttc cgt ctc aag tcc tgt gtg gat ttc      339
Ile Leu Tyr Ala Phe Glu Met Phe Arg Leu Lys Ser Cys Val Asp Phe
95                  100                 105                 110

aag ccc tat gaa gga gag agc tca tat atc ata ttt caa cag ttt gat      387
Lys Pro Tyr Glu Gly Glu Ser Ser Tyr Ile Ile Phe Gln Gln Phe Asp
                115                 120                 125

ggg tgc tgg tct gag gtt ggt gac caa cat gtg gga cag aac att tcc      435
Gly Cys Trp Ser Glu Val Gly Asp Gln His Val Gly Gln Asn Ile Ser
            130                 135                 140

att ggc caa gga tgt gcc tat aag gcc atc ata gaa cac gag atc ctg      483
Ile Gly Gln Gly Cys Ala Tyr Lys Ala Ile Ile Glu His Glu Ile Leu
        145                 150                 155

cat gct ttg gga ttt tac cac gag cag tca agg acg gac cgg gat gat      531
His Ala Leu Gly Phe Tyr His Glu Gln Ser Arg Thr Asp Arg Asp Asp
    160                 165                 170

tat gtg aac atc tgg tgg gac caa att ctt tca ggt tac cag cac aac      579
Tyr Val Asn Ile Trp Trp Asp Gln Ile Leu Ser Gly Tyr Gln His Asn
175                 180                 185                 190

ttt gac acc tat gat gat agc tta atc aca gac ctc aat aca ccc tat      627
Phe Asp Thr Tyr Asp Asp Ser Leu Ile Thr Asp Leu Asn Thr Pro Tyr
                195                 200                 205

gat tat gag tct ttg atg cac tac cag cct ttc tca ttt aac aag aat      675
Asp Tyr Glu Ser Leu Met His Tyr Gln Pro Phe Ser Phe Asn Lys Asn
            210                 215                 220

gca agt gtt ccc acc atc aca gcc aag atc cct gag ttt aac tcc att      723
Ala Ser Val Pro Thr Ile Thr Ala Lys Ile Pro Glu Phe Asn Ser Ile
        225                 230                 235

atc gga caa cgc ctg gat ttc agt gcc att gat tta gag agg ctg aac      771
Ile Gly Gln Arg Leu Asp Phe Ser Ala Ile Asp Leu Glu Arg Leu Asn
    240                 245                 250

cga atg tac aat tgc acc aca act cac act ctt ttg gac cac tgt act      819
Arg Met Tyr Asn Cys Thr Thr Thr His Thr Leu Leu Asp His Cys Thr
255                 260                 265                 270

ttt gag aag gca aac atc tgt gga atg att cag ggc acc aga gat gac      867
Phe Glu Lys Ala Asn Ile Cys Gly Met Ile Gln Gly Thr Arg Asp Asp
                275                 280                 285

act gac tgg gcc cat cag gac agt gct cag gct gga gaa gtg gat cac      915
Thr Asp Trp Ala His Gln Asp Ser Ala Gln Ala Gly Glu Val Asp His
            290                 295                 300

acc ttg ttg gga caa tgc aca ggt gcc ggc tac ttc atg cag ttc agc      963
Thr Leu Leu Gly Gln Cys Thr Gly Ala Gly Tyr Phe Met Gln Phe Ser
        305                 310                 315

acc agc tcg ggg tcc gcg gaa gag gca gcc cta ctg gag tct cgg att     1011
Thr Ser Ser Gly Ser Ala Glu Glu Ala Ala Leu Leu Glu Ser Arg Ile
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        320                 325                 330

ctt tac cca aag agg aag cag cag tgc ctg caa ttt ttc tat aaa atg      1059
Leu Tyr Pro Lys Arg Lys Gln Gln Cys Leu Gln Phe Phe Tyr Lys Met
335                 340                 345                 350

acg gga agt cct tca gac aga ctc gtt gtc tgg gtc agg agg gat gac      1107
Thr Gly Ser Pro Ser Asp Arg Leu Val Val Trp Val Arg Arg Asp Asp
                355                 360                 365

agc aca ggc aat gtt cgc aag ttg gtg aag gtg cag act ttt caa gga      1155
Ser Thr Gly Asn Val Arg Lys Leu Val Lys Val Gln Thr Phe Gln Gly
            370                 375                 380

gat gat gac cac aat tgg aaa att gcc cat gtg gtg ctc aaa gag gaa      1203
Asp Asp Asp His Asn Trp Lys Ile Ala His Val Val Leu Lys Glu Glu
        385                 390                 395

cag aag ttt cgc tac ctt ttc cag ggc aca aaa ggc gac cct cag aac      1251
Gln Lys Phe Arg Tyr Leu Phe Gln Gly Thr Lys Gly Asp Pro Gln Asn
    400                 405                 410

tca act ggg gga att tac cta gat gac atc act ctg aca gaa acc ccc      1299
Ser Thr Gly Gly Ile Tyr Leu Asp Asp Ile Thr Leu Thr Glu Thr Pro
415                 420                 425                 430

tgc ccc aca ggg gtc tgg aca gtc cgg aat ttc tcc caa gtc ctt gag      1347
Cys Pro Thr Gly Val Trp Thr Val Arg Asn Phe Ser Gln Val Leu Glu
                435                 440                 445

aac acc agc aaa ggg gac aag ctt cag agc cct cga ttc tac aat tcg      1395
Asn Thr Ser Lys Gly Asp Lys Leu Gln Ser Pro Arg Phe Tyr Asn Ser
            450                 455                 460

gag gga tat ggt ttt ggg gta act tta tac cca aat agc aga gaa agc      1443
Glu Gly Tyr Gly Phe Gly Val Thr Leu Tyr Pro Asn Ser Arg Glu Ser
        465                 470                 475

tct ggt tac ttg aga ctt gct ttt cat gtg tgc agt ggg gag aac gat      1491
Ser Gly Tyr Leu Arg Leu Ala Phe His Val Cys Ser Gly Glu Asn Asp
    480                 485                 490

gct atc ctg gag tgg ccg gta gaa aac aga cag gtg ata att acc atc      1539
Ala Ile Leu Glu Trp Pro Val Glu Asn Arg Gln Val Ile Ile Thr Ile
495                 500                 505                 510

ctt gac cag gag cct gat gtc cgg aac agg atg tcc tca agc atg gtg      1587
Leu Asp Gln Glu Pro Asp Val Arg Asn Arg Met Ser Ser Ser Met Val
                515                 520                 525

ttc act acc tcg aag tcg cac aca tct cca gcg ata aat gac act gtc      1635
Phe Thr Thr Ser Lys Ser His Thr Ser Pro Ala Ile Asn Asp Thr Val
            530                 535                 540

atc tgg gac agg ccg tcc agg gtg gga acc tat cat aca gac tgt aat      1683
Ile Trp Asp Arg Pro Ser Arg Val Gly Thr Tyr His Thr Asp Cys Asn
        545                 550                 555

tgt ttt aga agc atc gac ttg ggc tgg agt ggt ttc att tcc cac caa      1731
Cys Phe Arg Ser Ile Asp Leu Gly Trp Ser Gly Phe Ile Ser His Gln
    560                 565                 570

atg ctg aaa agg agg agt ttc ctg aaa aat gat gac ctc atc ata ttt      1779
Met Leu Lys Arg Arg Ser Phe Leu Lys Asn Asp Asp Leu Ile Ile Phe
575                 580                 585                 590

gtg gac ttt gaa gat atc acc cac ctc agc cag act gaa gtt ccc tct      1827
Val Asp Phe Glu Asp Ile Thr His Leu Ser Gln Thr Glu Val Pro Ser
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                  595                 600                 605

aaa ggc aaa aga ctg agc ccc caa ggc ctc att ctc caa ggc cag gag      1875
Lys Gly Lys Arg Leu Ser Pro Gln Gly Leu Ile Leu Gln Gly Gln Glu
            610                 615                 620

cag cag gtc tcc gaa gaa ggt tcg gga aag gcc atg tta gag gaa gcc      1923
Gln Gln Val Ser Glu Glu Gly Ser Gly Lys Ala Met Leu Glu Glu Ala
        625                 630                 635

cta cct gtc agc ctg agc cag ggg cag ccc agc cga cag aag cgg tcg      1971
Leu Pro Val Ser Leu Ser Gln Gly Gln Pro Ser Arg Gln Lys Arg Ser
    640                 645                 650

gtg gag aac aca ggc ccc ctg gag gac cat aac tgg cca cag tac ttc      2019
Val Glu Asn Thr Gly Pro Leu Glu Asp His Asn Trp Pro Gln Tyr Phe
655                 660                 665                 670

aga gac cca tgt gac cca aac cct tgc caa aat gac ggc atc tgt gtg      2067
Arg Asp Pro Cys Asp Pro Asn Pro Cys Gln Asn Asp Gly Ile Cys Val
                675                 680                 685

aac gtg aag ggg atg gcg agc tgc agg tgc atc tct gga cat gct ttc      2115
Asn Val Lys Gly Met Ala Ser Cys Arg Cys Ile Ser Gly His Ala Phe
            690                 695                 700

ttc tac acg ggg gag cgc tgt cag tcg gcc gag gtg cac ggc agt gtc      2163
Phe Tyr Thr Gly Glu Arg Cys Gln Ser Ala Glu Val His Gly Ser Val
        705                 710                 715

ctg ggc atg gtg atc gga ggc acg gct ggc gtg atc ttc ttg acc ttc      2211
Leu Gly Met Val Ile Gly Gly Thr Ala Gly Val Ile Phe Leu Thr Phe
    720                 725                 730

tcc atc atc gcc atc ctt tcc caa agg cca agg aag tgacctgcct           2257
Ser Ile Ile Ala Ile Leu Ser Gln Arg Pro Arg Lys
735                 740                 745

gctggcattg gccagaccac agcagcacct cctccatgca ggccttaact ttcccatgtt    2317

caatgcagtt tggggcagct tttttatcag ccttgctttg gataggacct ccaaggacta    2377

agcctccagc cccatgtgtg acccttgtca tctctctgcc ccacataatt atgttacttt    2437

gctatgtgct cctaatgtat ctagtgtgtc ctgtgacaac actcatcaca cttcattgta    2497

aatcacttgt tttattgact gtctttccta tagactgtaa gctccatgag ggcaggcaca    2557

tgttgttctc attgaccgtg ctggccccag tgcctagatg catggctggc acattgttgg    2617

cactcaacaa tggttgaatg aataaaacaa taaatgaatg aataactaag atatagaaac    2677

tctcatttat attgcagatt gaatatatat gatgaaattc ttatgttgaa tatgttagaa    2737

tcaaatactc atttttcatt agatacagta gtgtcatcac tcttttaaga tcttgttaaa    2797

gatttcaaat aaaggtactt ctggcgagcc aggctgcaca gcatttgctt tcctctgaga    2857

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Ala His Ile Ala Ala Val Pro Ile Lys His Leu Pro Glu Glu Asn Val
20 25 30

His Asp Ala Asp Phe Gly Glu Gln Lys Asp Ile Ser Glu Ile Asn Leu
35 40 45

Ala Ala Gly Leu Asp Leu Phe Gln Gly Asp Ile Leu Leu Gln Lys Ser
50 55 60

Arg Asn Gly Leu Arg Asp Pro Asn Thr Arg Trp Thr Phe Pro Ile Pro
65 70 75 80

Tyr Ile Leu Ala Asp Asn Leu Gly Leu Asn Ala Lys Gly Ala Ile Leu
85 90 95

Tyr Ala Phe Glu Met Phe Arg Leu Lys Ser Cys Val Asp Phe Lys Pro
100 105 110

Tyr Glu Gly Glu Ser Ser Tyr Ile Ile Phe Gln Gln Phe Asp Gly Cys
115 120 125

Trp Ser Glu Val Gly Asp Gln His Val Gly Gln Asn Ile Ser Ile Gly
130 135 140

Gln Gly Cys Ala Tyr Lys Ala Ile Ile Glu His Glu Ile Leu His Ala
145 150 155 160

Leu Gly Phe Tyr His Glu Gln Ser Arg Thr Asp Arg Asp Asp Tyr Val
165 170 175

Asn Ile Trp Trp Asp Gln Ile Leu Ser Gly Tyr Gln His Asn Phe Asp
180 185 190

Thr Tyr Asp Asp Ser Leu Ile Thr Asp Leu Asn Thr Pro Tyr Asp Tyr
195 200 205

Glu Ser Leu Met His Tyr Gln Pro Phe Ser Phe Asn Lys Asn Ala Ser
210 215 220

Val Pro Thr Ile Thr Ala Lys Ile Pro Glu Phe Asn Ser Ile Ile Gly
225 230 235 240

Gln Arg Leu Asp Phe Ser Ala Ile Asp Leu Glu Arg Leu Asn Arg Met
245 250 255

Tyr Asn Cys Thr Thr Thr His Thr Leu Leu Asp His Cys Thr Phe Glu
260 265 270

Lys Ala Asn Ile Cys Gly Met Ile Gln Gly Thr Arg Asp Asp Thr Asp
275 280 285

Trp Ala His Gln Asp Ser Ala Gln Ala Gly Glu Val Asp His Thr Leu
290 295 300

Leu Gly Gln Cys Thr Gly Ala Gly Tyr Phe Met Gln Phe Ser Thr Ser
305 310 315 320

Ser Gly Ser Ala Glu Glu Ala Ala Leu Leu Glu Ser Arg Ile Leu Tyr
325 330 335

Pro Lys Arg Lys Gln Gln Cys Leu Gln Phe Phe Tyr Lys Met Thr Gly
340 345 350

Ser Pro Ser Asp Arg Leu Val Val Trp Val Arg Arg Asp Asp Ser Thr
355 360 365

Gly Asn Val Arg Lys Leu Val Lys Val Gln Thr Phe Gln Gly Asp Asp
370 375 380

Asp His Asn Trp Lys Ile Ala His Val Val Leu Lys Glu Glu Gln Lys
385 390 395 400

Phe Arg Tyr Leu Phe Gln Gly Thr Lys Gly Asp Pro Gln Asn Ser Thr
405 410 415

Gly Gly Ile Tyr Leu Asp Asp Ile Thr Leu Thr Glu Thr Pro Cys Pro
420 425 430

Thr Gly Val Trp Thr Val Arg Asn Phe Ser Gln Val Leu Glu Asn Thr
435 440 445

Ser Lys Gly Asp Lys Leu Gln Ser Pro Arg Phe Tyr Asn Ser Glu Gly
450 455 460

Tyr Gly Phe Gly Val Thr Leu Tyr Pro Asn Ser Arg Glu Ser Ser Gly
465 470 475 480

Tyr Leu Arg Leu Ala Phe His Val Cys Ser Gly Glu Asn Asp Ala Ile
485 490 495

Leu Glu Trp Pro Val Glu Asn Arg Gln Val Ile Ile Thr Ile Leu Asp
500 505 510

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Gln Glu Pro Asp Val Arg Asn Arg Met Ser Ser Ser Met Val Phe Thr
        515                 520                 525

Thr Ser Lys Ser His Thr Ser Pro Ala Ile Asn Asp Thr Val Ile Trp
    530                 535                 540

Asp Arg Pro Ser Arg Val Gly Thr Tyr His Thr Asp Cys Asn Cys Phe
545                 550                 555                 560

Arg Ser Ile Asp Leu Gly Trp Ser Gly Phe Ile Ser His Gln Met Leu
                565                 570                 575

Lys Arg Arg Ser Phe Leu Lys Asn Asp Asp Leu Ile Ile Phe Val Asp
            580                 585                 590

Phe Glu Asp Ile Thr His Leu Ser Gln Thr Glu Val Pro Ser Lys Gly
        595                 600                 605

Lys Arg Leu Ser Pro Gln Gly Leu Ile Leu Gln Gly Gln Glu Gln Gln
    610                 615                 620

Val Ser Glu Glu Gly Ser Gly Lys Ala Met Leu Glu Glu Ala Leu Pro
625                 630                 635                 640

Val Ser Leu Ser Gln Gly Gln Pro Ser Arg Gln Lys Arg Ser Val Glu
                645                 650                 655

Asn Thr Gly Pro Leu Glu Asp His Asn Trp Pro Gln Tyr Phe Arg Asp
            660                 665                 670

Pro Cys Asp Pro Asn Pro Cys Gln Asn Asp Gly Ile Cys Val Asn Val
        675                 680                 685

Lys Gly Met Ala Ser Cys Arg Cys Ile Ser Gly His Ala Phe Phe Tyr
    690                 695                 700

Thr Gly Glu Arg Cys Gln Ser Ala Glu Val His Gly Ser Val Leu Gly
705                 710                 715                 720

Met Val Ile Gly Gly Thr Ala Gly Val Ile Phe Leu Thr Phe Ser Ile
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Ile Ala Ile Leu Ser Gln Arg Pro Arg Lys
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Val His Pro Leu Pro Gly Thr Glu Asp Gln Leu Asn Asp Arg Leu Arg
10 15 20

gaa gtt tct gag aag ctg aac aaa tat aat tta aac agc cac ccc cct 150
Glu Val Ser Glu Lys Leu Asn Lys Tyr Asn Leu Asn Ser His Pro Pro
25 30 35

ttg aat gta ttg gaa cag gct act att aaa cag tgt gtg gtg gga cca 198
Leu Asn Val Leu Glu Gln Ala Thr Ile Lys Gln Cys Val Val Gly Pro
40 45 50 55

aat cat gct gcc ttt ctt ctt gag gat ggt aga gtt tgc agg att ggt 246
Asn His Ala Ala Phe Leu Leu Glu Asp Gly Arg Val Cys Arg Ile Gly
60 65 70

ttt tca gta cag cca gac aga ttg gaa ttg ggt aaa cct gat aat aat 294
Phe Ser Val Gln Pro Asp Arg Leu Glu Leu Gly Lys Pro Asp Asn Asn
75 80 85

gat ggg tca aag ttg aac agc aac tcg ggg gca ggg agg acg tca agg 342
Asp Gly Ser Lys Leu Asn Ser Asn Ser Gly Ala Gly Arg Thr Ser Arg
90 95 100

cct ggt agg aca agc gac tct cca tgg ttt ctc tca ggt tct gag act 390
Pro Gly Arg Thr Ser Asp Ser Pro Trp Phe Leu Ser Gly Ser Glu Thr
105 110 115

cta ggc agg ctg gca ggc aac acc tta gga agc cgc tgg agt tct gga 438
Leu Gly Arg Leu Ala Gly Asn Thr Leu Gly Ser Arg Trp Ser Ser Gly
120 125 130 135

gtg ggt gga agt ggt gga gga tcc tct ggt agg tca tca gct gga gct 486
Val Gly Gly Ser Gly Gly Gly Ser Ser Gly Arg Ser Ser Ala Gly Ala
140 145 150

cga gat tcc cgc cgg cag act cga gtt att cgg aca gga cgg gat cga 534
Arg Asp Ser Arg Arg Gln Thr Arg Val Ile Arg Thr Gly Arg Asp Arg
155 160 165

ggg tct ggg ctt ttg ggc agt cag ccc cag cca gtt att cca gca tct 582
Gly Ser Gly Leu Leu Gly Ser Gln Pro Gln Pro Val Ile Pro Ala Ser
170 175 180

gtc att cca gag gag ctg att tca cag gcc caa gtt gtt tta caa ggc 630
Val Ile Pro Glu Glu Leu Ile Ser Gln Ala Gln Val Val Leu Gln Gly
185 190 195

aaa tcc aga agt gtc att att cga gaa ctt cag aga aca aat ctt gat 678
Lys Ser Arg Ser Val Ile Ile Arg Glu Leu Gln Arg Thr Asn Leu Asp
200 205 210 215

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gtg aac ctt gct gta aat aat tta ctt agc cgg gat gat gaa gat gga      726
Val Asn Leu Ala Val Asn Asn Leu Leu Ser Arg Asp Asp Glu Asp Gly
                220                 225                 230

gat gat ggg gat gat aca gcc agc gaa tct tat ttg cct gga gag gat      774
Asp Asp Gly Asp Asp Thr Ala Ser Glu Ser Tyr Leu Pro Gly Glu Asp
            235                 240                 245

ctt atg tct ctc ctt gat gcc gac att cat tct gcc cac cca agt gtc      822
Leu Met Ser Leu Leu Asp Ala Asp Ile His Ser Ala His Pro Ser Val
        250                 255                 260

att att gat gca gat gcc atg ttt tct gaa gac att agc tat ttt ggt      870
Ile Ile Asp Ala Asp Ala Met Phe Ser Glu Asp Ile Ser Tyr Phe Gly
    265                 270                 275

tac cct tct ttt cgt cgt tca tca ctt tcc agg cta ggc tca tct cga      918
Tyr Pro Ser Phe Arg Arg Ser Ser Leu Ser Arg Leu Gly Ser Ser Arg
280                 285                 290                 295

gtt ctc ctt ctt ccc tta gag aga gac tct gag ctg ttg cgt gaa cgt      966
Val Leu Leu Leu Pro Leu Glu Arg Asp Ser Glu Leu Leu Arg Glu Arg
                300                 305                 310

gaa tcc gtt tta cgt tta cgt gaa cga agg tgg ctt gat gga gcc tca     1014
Glu Ser Val Leu Arg Leu Arg Glu Arg Arg Trp Leu Asp Gly Ala Ser
            315                 320                 325

ttt gat aat gaa agg ggt tct acc agc aag gaa gga gag cca aac ttg     1062
Phe Asp Asn Glu Arg Gly Ser Thr Ser Lys Glu Gly Glu Pro Asn Leu
        330                 335                 340

gat aag aag aat aca cct gtt caa agt cca gta tct cta gga gaa gat     1110
Asp Lys Lys Asn Thr Pro Val Gln Ser Pro Val Ser Leu Gly Glu Asp
    345                 350                 355

ttg cag tgg tgg cct gat aag gat gga aca aaa ttc atc tgt att ggg     1158
Leu Gln Trp Trp Pro Asp Lys Asp Gly Thr Lys Phe Ile Cys Ile Gly
360                 365                 370                 375

gct ctg tat tct gaa ctt ctg gct gtc agc agt aaa gga gaa ctt tat     1206
Ala Leu Tyr Ser Glu Leu Leu Ala Val Ser Ser Lys Gly Glu Leu Tyr
                380                 385                 390

cag tgg aaa tgg agt gaa tct gag cct tac aga aat gcc cag aat cct     1254
Gln Trp Lys Trp Ser Glu Ser Glu Pro Tyr Arg Asn Ala Gln Asn Pro
            395                 400                 405

tca tta cat cat cca cga gca aca ttt ttg ggg tta acc aat gaa aag     1302
Ser Leu His His Pro Arg Ala Thr Phe Leu Gly Leu Thr Asn Glu Lys
        410                 415                 420

ata gtc ctc ctg tct gca aat agc ata aga gca act gta gct aca gaa     1350
Ile Val Leu Leu Ser Ala Asn Ser Ile Arg Ala Thr Val Ala Thr Glu
    425                 430                 435

aat aac aag gtt gct aca tgg gtg gat gaa act tta agt tct gtg gct     1398
Asn Asn Lys Val Ala Thr Trp Val Asp Glu Thr Leu Ser Ser Val Ala
440                 445                 450                 455

tct aaa tta gag cac act gct cag act tac tct gaa ctt caa gga gag     1446
Ser Lys Leu Glu His Thr Ala Gln Thr Tyr Ser Glu Leu Gln Gly Glu
                460                 465                 470

cgg ata gtt tct tta cat tgc tgt gcc ctt tac acc tgc gct cag ctg     1494
Arg Ile Val Ser Leu His Cys Cys Ala Leu Tyr Thr Cys Ala Gln Leu
            475                 480                 485
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gaa aac agt tta tat tgg tgg ggt gta gtt cct ttt agt caa agg aag      1542
Glu Asn Ser Leu Tyr Trp Trp Gly Val Val Pro Phe Ser Gln Arg Lys
        490                 495                 500

aaa atg tta gag aaa gct aga gca aaa aat aaa aag cct aaa tcc agt      1590
Lys Met Leu Glu Lys Ala Arg Ala Lys Asn Lys Lys Pro Lys Ser Ser
    505                 510                 515

gct ggt att tct tca atg ccg aac atc act gtt ggt acc cag gta tgc      1638
Ala Gly Ile Ser Ser Met Pro Asn Ile Thr Val Gly Thr Gln Val Cys
520                 525                 530                 535

ttg aga aat aat cct ctt tat cat gct gga gca gtt gca ttt tca att      1686
Leu Arg Asn Asn Pro Leu Tyr His Ala Gly Ala Val Ala Phe Ser Ile
                540                 545                 550

agt gct ggg att cct aaa gtt ggt gtc tta atg gag tca gtt tgg aat      1734
Ser Ala Gly Ile Pro Lys Val Gly Val Leu Met Glu Ser Val Trp Asn
            555                 560                 565

atg aat gac agc tgt aga ttt caa ctt aga tct cct gaa agc ttg aaa      1782
Met Asn Asp Ser Cys Arg Phe Gln Leu Arg Ser Pro Glu Ser Leu Lys
        570                 575                 580

aac atg gaa aaa gct agc aaa act act gaa gct aag cct gaa agt aag      1830
Asn Met Glu Lys Ala Ser Lys Thr Thr Glu Ala Lys Pro Glu Ser Lys
    585                 590                 595

cag gag cca gtg aaa aca gaa atg ggt cct cca cca tct cca gca tcc      1878
Gln Glu Pro Val Lys Thr Glu Met Gly Pro Pro Pro Ser Pro Ala Ser
600                 605                 610                 615

acg tgt agt gat gca tcc tca att gcc agc agt gca tca atg cca tac      1926
Thr Cys Ser Asp Ala Ser Ser Ile Ala Ser Ser Ala Ser Met Pro Tyr
                620                 625                 630

aaa cga cga cgg tca acc cct gca cca aaa gaa gag gaa aag gtg aat      1974
Lys Arg Arg Arg Ser Thr Pro Ala Pro Lys Glu Glu Glu Lys Val Asn
            635                 640                 645

gaa gag cag tgg tct ctt cgg gaa gtg gtt ttt gtg gaa gat gtc aag      2022
Glu Glu Gln Trp Ser Leu Arg Glu Val Val Phe Val Glu Asp Val Lys
        650                 655                 660

aat gtt cct gtt ggc aag gtg cta aaa gta gat ggt gcc tat gtt gct      2070
Asn Val Pro Val Gly Lys Val Leu Lys Val Asp Gly Ala Tyr Val Ala
    665                 670                 675

gta aaa ttt cca gga acc tcc agt aat act aac tgt cag aac agc tct      2118
Val Lys Phe Pro Gly Thr Ser Ser Asn Thr Asn Cys Gln Asn Ser Ser
680                 685                 690                 695

ggt cca gat gct gac cct tct tct ctc ctg cag gat tgt agg tta ctt      2166
Gly Pro Asp Ala Asp Pro Ser Ser Leu Leu Gln Asp Cys Arg Leu Leu
                700                 705                 710

aga att gat gaa ttg cag gtt gtc aaa act ggt gga aca ccg aag gtt      2214
Arg Ile Asp Glu Leu Gln Val Val Lys Thr Gly Gly Thr Pro Lys Val
            715                 720                 725

ccc gac tgt ttc caa agg act cct aaa aag ctt tgt ata cct gaa aaa      2262
Pro Asp Cys Phe Gln Arg Thr Pro Lys Lys Leu Cys Ile Pro Glu Lys
        730                 735                 740

aca gaa ata tta gca gtg aat gta gat tcc aaa ggt gtt cat gct gtt      2310
Thr Glu Ile Leu Ala Val Asn Val Asp Ser Lys Gly Val His Ala Val
    745                 750                 755
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ctg aag act gga aat tgg gtg cga tac tgt atc ttt gat ctt gct aca      2358
Leu Lys Thr Gly Asn Trp Val Arg Tyr Cys Ile Phe Asp Leu Ala Thr
760                 765                 770                 775

gga aaa gca gaa cag gaa aat aat ttt cct aca agc agc att gct ttc      2406
Gly Lys Ala Glu Gln Glu Asn Asn Phe Pro Thr Ser Ser Ile Ala Phe
            780                 785                 790

ctt ggt cag aat gag agg aat gta gcc att ttc act gct gga cag gaa      2454
Leu Gly Gln Asn Glu Arg Asn Val Ala Ile Phe Thr Ala Gly Gln Glu
        795                 800                 805

tct ccc att att ctt cga gat gga aat ggt acc atc tac cca atg gcc      2502
Ser Pro Ile Ile Leu Arg Asp Gly Asn Gly Thr Ile Tyr Pro Met Ala
    810                 815                 820

aaa gat tgc atg gga gga ata agg gat ccc gat tgg ctg gat ctt cca      2550
Lys Asp Cys Met Gly Gly Ile Arg Asp Pro Asp Trp Leu Asp Leu Pro
825                 830                 835

cct att agt agt ctt gga atg ggt gtg cat tct tta ata aat ctt cct      2598
Pro Ile Ser Ser Leu Gly Met Gly Val His Ser Leu Ile Asn Leu Pro
840                 845                 850                 855

gcc aat tca aca atc aaa aag aaa gct gct gtt atc atc atg gct gta      2646
Ala Asn Ser Thr Ile Lys Lys Lys Ala Ala Val Ile Ile Met Ala Val
            860                 865                 870

gag aaa caa acc tta atg caa cac att ctg cgc tgt gac tat gag gcc      2694
Glu Lys Gln Thr Leu Met Gln His Ile Leu Arg Cys Asp Tyr Glu Ala
        875                 880                 885

tgt cga caa tat cta atg aat ctt gag caa gcg gtt gtt tta gag cag      2742
Cys Arg Gln Tyr Leu Met Asn Leu Glu Gln Ala Val Val Leu Glu Gln
    890                 895                 900

aat cta cag atg ctg cag aca ttc atc agc cac aga tgt gat gga aat      2790
Asn Leu Gln Met Leu Gln Thr Phe Ile Ser His Arg Cys Asp Gly Asn
905                 910                 915

cga aat att ttg cat gct tgt gta tca gtt tgc ttt cca acc agc aat      2838
Arg Asn Ile Leu His Ala Cys Val Ser Val Cys Phe Pro Thr Ser Asn
920                 925                 930                 935

aaa gaa act aaa gaa gaa gag gaa gcg gag cgt tct gaa aga aat aca      2886
Lys Glu Thr Lys Glu Glu Glu Glu Ala Glu Arg Ser Glu Arg Asn Thr
            940                 945                 950

ttt gca gaa agg ctt tct gct gtt gag gcc att gca aat gca ata tca      2934
Phe Ala Glu Arg Leu Ser Ala Val Glu Ala Ile Ala Asn Ala Ile Ser
        955                 960                 965

gtt gtt tca agt aat ggc cca ggt aat cgg gct gga tca tca agt agc      2982
Val Val Ser Ser Asn Gly Pro Gly Asn Arg Ala Gly Ser Ser Ser Ser
    970                 975                 980

cga agt ttg aga tta cgg gaa atg atg aga cgt tcg ttg aga gca gct      3030
Arg Ser Leu Arg Leu Arg Glu Met Met Arg Arg Ser Leu Arg Ala Ala
985                 990                 995

ggt  ttg ggt aga cat gaa  gct gga gct tca tcc  agt gac cac cag       3075
Gly  Leu Gly Arg His Glu  Ala Gly Ala Ser Ser  Ser Asp His Gln
1000                 1005                 1010

gat  cca gtt tca ccc ccc  ata gct ccc cct agt  tgg gtt cct gac       3120
Asp  Pro Val Ser Pro Pro  Ile Ala Pro Pro Ser  Trp Val Pro Asp
1015                 1020                 1025
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cct  cct gcg atg gat cct  gat ggt gac att gat  ttt atc ctg gcc      3165
Pro  Pro Ala Met Asp Pro  Asp Gly Asp Ile Asp  Phe Ile Leu Ala
1030                 1035                 1040

ccc  gct gtg gga tct ctt  acc aca gca gca acc  ggt act ggt caa      3210
Pro  Ala Val Gly Ser Leu  Thr Thr Ala Ala Thr  Gly Thr Gly Gln
1045                 1050                 1055

gga  cca agc acc tcc act  att cca ggt cct tcc  aca gag cca tct      3255
Gly  Pro Ser Thr Ser Thr  Ile Pro Gly Pro Ser  Thr Glu Pro Ser
1060                 1065                 1070

gta  gta gaa tcc aag gat  cga aag gcg aat gct  cat ttt ata ttg      3300
Val  Val Glu Ser Lys Asp  Arg Lys Ala Asn Ala  His Phe Ile Leu
1075                 1080                 1085

aaa  ttg tta tgt gac agt  gtg gtt ctc cag ccc  tat cta cga gaa      3345
Lys  Leu Leu Cys Asp Ser  Val Val Leu Gln Pro  Tyr Leu Arg Glu
1090                 1095                 1100

ctt  ctt tct gcc aag gat  gca aga ggg atg acc  cca ttt atg tca      3390
Leu  Leu Ser Ala Lys Asp  Ala Arg Gly Met Thr  Pro Phe Met Ser
1105                 1110                 1115

gct  gta agt ggc cga gct  tat cct gct gca att  acc atc tta gaa      3435
Ala  Val Ser Gly Arg Ala  Tyr Pro Ala Ala Ile  Thr Ile Leu Glu
1120                 1125                 1130

act  gct cag aaa att gca  aaa gct gaa ata tcc  tca agt gaa aaa      3480
Thr  Ala Gln Lys Ile Ala  Lys Ala Glu Ile Ser  Ser Ser Glu Lys
1135                 1140                 1145

gag  gaa gat gta ttc atg  gga atg gtt tgc cca  tca ggt acc aac      3525
Glu  Glu Asp Val Phe Met  Gly Met Val Cys Pro  Ser Gly Thr Asn
1150                 1155                 1160

cct  gat gac tct cct tta  tat gtt tta tgt tgt  aat gac act tgc      3570
Pro  Asp Asp Ser Pro Leu  Tyr Val Leu Cys Cys  Asn Asp Thr Cys
1165                 1170                 1175

agt  ttt aca tgg act gga  gca gag cac att aac  cag gat att ttt      3615
Ser  Phe Thr Trp Thr Gly  Ala Glu His Ile Asn  Gln Asp Ile Phe
1180                 1185                 1190

gag  tgt cga act tgt ggc  ttg ctg gag tca ctg  tgt tgt tgt acg      3660
Glu  Cys Arg Thr Cys Gly  Leu Leu Glu Ser Leu  Cys Cys Cys Thr
1195                 1200                 1205

gaa  tgt gca agg gtt tgt  cat aaa ggt cat gat  tgc aaa ctc aaa      3705
Glu  Cys Ala Arg Val Cys  His Lys Gly His Asp  Cys Lys Leu Lys
1210                 1215                 1220

cgg  aca tca cca aca gcc  tac tgt gat tgt tgg  gag aaa tgt aaa      3750
Arg  Thr Ser Pro Thr Ala  Tyr Cys Asp Cys Trp  Glu Lys Cys Lys
1225                 1230                 1235

tgt  aaa act ctt att gct  gga cag aaa tct gct  cgt ctt gat cta      3795
Cys  Lys Thr Leu Ile Ala  Gly Gln Lys Ser Ala  Arg Leu Asp Leu
1240                 1245                 1250

ctt  tat cgc ctg ctc act  gct act aat ctg gtt  act ctg cca aac      3840
Leu  Tyr Arg Leu Leu Thr  Ala Thr Asn Leu Val  Thr Leu Pro Asn
1255                 1260                 1265

agc  agg gga gag cac ctc  tta cta ttc tta gta  cag aca gtc gca      3885
Ser  Arg Gly Glu His Leu  Leu Leu Phe Leu Val  Gln Thr Val Ala
1270                 1275                 1280
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agg cag acg gtg gag cat tgt caa tac agg cca cct cga atc agg 3930
Arg Gln Thr Val Glu His Cys Gln Tyr Arg Pro Pro Arg Ile Arg
1285 1290 1295

gaa gat cgt aac cga aaa aca gcc agt cct gaa gat tca gat atg 3975
Glu Asp Arg Asn Arg Lys Thr Ala Ser Pro Glu Asp Ser Asp Met
1300 1305 1310

cca gat cat gat tta gag cct cca aga ttt gcc cag ctt gca ttg 4020
Pro Asp His Asp Leu Glu Pro Pro Arg Phe Ala Gln Leu Ala Leu
1315 1320 1325

gag cgt gtt cta cag gac tgg aat gcc ttg aaa tct atg att atg 4065
Glu Arg Val Leu Gln Asp Trp Asn Ala Leu Lys Ser Met Ile Met
1330 1335 1340

ttt ggg tcg cag gag aat aaa gac cct ctt agt gcc agc agt aga 4110
Phe Gly Ser Gln Glu Asn Lys Asp Pro Leu Ser Ala Ser Ser Arg
1345 1350 1355

ata ggc cat ctt ttg cca gaa gag caa gta tac ctc aat cag caa 4155
Ile Gly His Leu Leu Pro Glu Glu Gln Val Tyr Leu Asn Gln Gln
1360 1365 1370

agt ggc aca att cgg ctg gac tgt ttc act cat tgc ctt ata gtt 4200
Ser Gly Thr Ile Arg Leu Asp Cys Phe Thr His Cys Leu Ile Val
1375 1380 1385

aag tgt aca gca gat att ttg ctt tta gat act cta cta ggt aca 4245
Lys Cys Thr Ala Asp Ile Leu Leu Leu Asp Thr Leu Leu Gly Thr
1390 1395 1400

cta gtg aaa gaa ctc caa aac aaa tat aca cct gga cgt aga gaa 4290
Leu Val Lys Glu Leu Gln Asn Lys Tyr Thr Pro Gly Arg Arg Glu
1405 1410 1415

gaa gct att gct gtg aca atg agg ttt cta cgt tca gtg gca aga 4335
Glu Ala Ile Ala Val Thr Met Arg Phe Leu Arg Ser Val Ala Arg
1420 1425 1430

gtt ttt gtt att ctg agt gtg gaa atg gct tca tcc aaa aag aaa 4380
Val Phe Val Ile Leu Ser Val Glu Met Ala Ser Ser Lys Lys Lys
1435 1440 1445

aac aac ttt att cca cag cca att gga aaa tgc aag cgt gta ttc 4425
Asn Asn Phe Ile Pro Gln Pro Ile Gly Lys Cys Lys Arg Val Phe
1450 1455 1460

caa gca ttg cta cct tac gct gtg gaa gaa ttg tgc aac gta gca 4470
Gln Ala Leu Leu Pro Tyr Ala Val Glu Glu Leu Cys Asn Val Ala
1465 1470 1475

gag tca ctg att gtt cct gtc aga atg ggg att gct cgt cca act 4515
Glu Ser Leu Ile Val Pro Val Arg Met Gly Ile Ala Arg Pro Thr
1480 1485 1490

gca cca ttt acc ctg gct agt act agc ata gat gcc atg cag ggc 4560
Ala Pro Phe Thr Leu Ala Ser Thr Ser Ile Asp Ala Met Gln Gly
1495 1500 1505

agt gaa gaa tta ttt tca gtg gaa cca cta cca cca cga cca tca 4605
Ser Glu Glu Leu Phe Ser Val Glu Pro Leu Pro Pro Arg Pro Ser
1510 1515 1520

tct gat cag tct agc agc tcc agt cag tct cag tca tcc tac atc 4650
Ser Asp Gln Ser Ser Ser Ser Ser Gln Ser Gln Ser Ser Tyr Ile
1525 1530 1535

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atc agg aat cca cag cag agg cgc atc agc cag tca cag ccc gtt      4695
Ile Arg Asn Pro Gln Gln Arg Arg Ile Ser Gln Ser Gln Pro Val
1540                1545                1550

cgg ggc aga gat gaa gaa cag gat gat att gtt tca gca gat gtg      4740
Arg Gly Arg Asp Glu Glu Gln Asp Asp Ile Val Ser Ala Asp Val
1555                1560                1565

gaa gag gtt gag gtg gtg gag ggt gtg gct gga gaa gag gat cat      4785
Glu Glu Val Glu Val Val Glu Gly Val Ala Gly Glu Glu Asp His
1570                1575                1580

cat gat gaa cag gaa gaa cac ggg gaa gaa aat gct gag gca gag      4830
His Asp Glu Gln Glu Glu His Gly Glu Glu Asn Ala Glu Ala Glu
1585                1590                1595

gga caa cat gat gag cat gat gaa gac ggg agt gat atg gag ctg      4875
Gly Gln His Asp Glu His Asp Glu Asp Gly Ser Asp Met Glu Leu
1600                1605                1610

gac ttg tta gca gca gct gaa aca gaa agt gat agt gaa agt aac      4920
Asp Leu Leu Ala Ala Ala Glu Thr Glu Ser Asp Ser Glu Ser Asn
1615                1620                1625

cac agc aac caa gat aat gct agt ggg cgc aga agc gtt gtc act      4965
His Ser Asn Gln Asp Asn Ala Ser Gly Arg Arg Ser Val Val Thr
1630                1635                1640

gca gca act gct ggt tca gaa gca gga gca agc agt gtt cct gcc      5010
Ala Ala Thr Ala Gly Ser Glu Ala Gly Ala Ser Ser Val Pro Ala
1645                1650                1655

ttc ttt tct gaa gat gat tct caa tcg aat gac tca agt gat tct      5055
Phe Phe Ser Glu Asp Asp Ser Gln Ser Asn Asp Ser Ser Asp Ser
1660                1665                1670

gat agc agt agt agt cag agt gac gac ata gaa cag gag acc ttt      5100
Asp Ser Ser Ser Ser Gln Ser Asp Asp Ile Glu Gln Glu Thr Phe
1675                1680                1685

atg ctt gat gag cca tta gaa aga acc aca aat agc tcc cat gcc      5145
Met Leu Asp Glu Pro Leu Glu Arg Thr Thr Asn Ser Ser His Ala
1690                1695                1700

aat ggt gct gcc caa gct ccc cgt tca atg cag tgg gct gtc cgc      5190
Asn Gly Ala Ala Gln Ala Pro Arg Ser Met Gln Trp Ala Val Arg
1705                1710                1715

aac acc cag cat cag cga gca gcc agt aca gcc cct tcc agt aca      5235
Asn Thr Gln His Gln Arg Ala Ala Ser Thr Ala Pro Ser Ser Thr
1720                1725                1730

tct aca cca gca gca agt tca gcg ggt ttg att tat att gat cct      5280
Ser Thr Pro Ala Ala Ser Ser Ala Gly Leu Ile Tyr Ile Asp Pro
1735                1740                1745

tca aac tta cgc cgg agt ggt acc atc agt aca agt gct gca gct      5325
Ser Asn Leu Arg Arg Ser Gly Thr Ile Ser Thr Ser Ala Ala Ala
1750                1755                1760

gca gca gct gct ttg gaa gct agc aac gcc agc agt tac cta aca      5370
Ala Ala Ala Ala Leu Glu Ala Ser Asn Ala Ser Ser Tyr Leu Thr
1765                1770                1775

tct gca agc agt tta gcc agg gct tac agc att gtc att aga caa      5415
Ser Ala Ser Ser Leu Ala Arg Ala Tyr Ser Ile Val Ile Arg Gln
1780                1785                1790
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atc tcg gac ttg atg ggc ctt att cct aag tat aat cac cta gta    5460
Ile Ser Asp Leu Met Gly Leu Ile Pro Lys Tyr Asn His Leu Val
1795                1800                1805

tac tct cag att cca gca gct gtg aaa ttg act tac caa gat gca    5505
Tyr Ser Gln Ile Pro Ala Ala Val Lys Leu Thr Tyr Gln Asp Ala
1810                1815                1820

gta aac tta cag aac tat gta gaa gaa aag ctt att ccc act tgg    5550
Val Asn Leu Gln Asn Tyr Val Glu Glu Lys Leu Ile Pro Thr Trp
1825                1830                1835

aac tgg atg gtc agt att atg gat tct act gaa gct caa tta cgt    5595
Asn Trp Met Val Ser Ile Met Asp Ser Thr Glu Ala Gln Leu Arg
1840                1845                1850

tat ggt tct gca tta gca tct gct ggt gat cct gga cat cca aat    5640
Tyr Gly Ser Ala Leu Ala Ser Ala Gly Asp Pro Gly His Pro Asn
1855                1860                1865

cat cct ctt cac gct tct cag aat tca gcg aga aga gag agg atg    5685
His Pro Leu His Ala Ser Gln Asn Ser Ala Arg Arg Glu Arg Met
1870                1875                1880

act gcg cga gaa gaa gct agc tta cga aca ctt gaa ggc aga cga    5730
Thr Ala Arg Glu Glu Ala Ser Leu Arg Thr Leu Glu Gly Arg Arg
1885                1890                1895

cgt gcc acc ttg ctt agc gcc cgt caa gga atg atg tct gca cga    5775
Arg Ala Thr Leu Leu Ser Ala Arg Gln Gly Met Met Ser Ala Arg
1900                1905                1910

gga gac ttc cta aat tat gct ctg tct cta atg cgg tct cat aat    5820
Gly Asp Phe Leu Asn Tyr Ala Leu Ser Leu Met Arg Ser His Asn
1915                1920                1925

gat gag cat tct gat gtt ctt cca gtt ttg gat gtt tgc tca ttg    5865
Asp Glu His Ser Asp Val Leu Pro Val Leu Asp Val Cys Ser Leu
1930                1935                1940

aag cat gtg gca tat gtt ttt caa gca ctt ata tac tgg att aag    5910
Lys His Val Ala Tyr Val Phe Gln Ala Leu Ile Tyr Trp Ile Lys
1945                1950                1955

gca atg aat cag cag aca aca ttg gat aca cct caa cta gaa cgc    5955
Ala Met Asn Gln Gln Thr Thr Leu Asp Thr Pro Gln Leu Glu Arg
1960                1965                1970

aaa agg acg cga gaa ctc ttg gaa ctg ggt att gat aat gaa gat    6000
Lys Arg Thr Arg Glu Leu Leu Glu Leu Gly Ile Asp Asn Glu Asp
1975                1980                1985

tca gaa cat gaa aat gat gat gac acc aat caa agt gct act ttg    6045
Ser Glu His Glu Asn Asp Asp Asp Thr Asn Gln Ser Ala Thr Leu
1990                1995                2000

aat gat aag gat gat gac tct ctt cct gca gaa act ggc caa aac    6090
Asn Asp Lys Asp Asp Asp Ser Leu Pro Ala Glu Thr Gly Gln Asn
2005                2010                2015

cat cca ttt ttc cga cgt tca gac tcc atg aca ttc ctt ggg tgt    6135
His Pro Phe Phe Arg Arg Ser Asp Ser Met Thr Phe Leu Gly Cys
2020                2025                2030

ata ccc cca aat cca ttt gaa gtg cct ctg gct gaa gcc atc ccc    6180
Ile Pro Pro Asn Pro Phe Glu Val Pro Leu Ala Glu Ala Ile Pro
2035                2040                2045
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ttg gct gat cag cca cat ctg ttg cag cca aat gct aga aag gag 6225
Leu Ala Asp Gln Pro His Leu Leu Gln Pro Asn Ala Arg Lys Glu
2050 2055 2060

gat ctt ttt ggc cgt cca agt cag ggt ctt tat tct tca tct gcc 6270
Asp Leu Phe Gly Arg Pro Ser Gln Gly Leu Tyr Ser Ser Ser Ala
2065 2070 2075

agt agt ggg aaa tgt tta atg gag gtt aca gtg gat aga aac tgc 6315
Ser Ser Gly Lys Cys Leu Met Glu Val Thr Val Asp Arg Asn Cys
2080 2085 2090

cta gag gtt ctt cca aca aaa atg tct tat gct gcc aat ctg aaa 6360
Leu Glu Val Leu Pro Thr Lys Met Ser Tyr Ala Ala Asn Leu Lys
2095 2100 2105

aat gta atg aac atg caa aac cgg caa aaa aaa gaa ggg gaa gaa 6405
Asn Val Met Asn Met Gln Asn Arg Gln Lys Lys Glu Gly Glu Glu
2110 2115 2120

cag ccc gtg ctg cca gaa gaa act gag agt tca aaa cca ggg cca 6450
Gln Pro Val Leu Pro Glu Glu Thr Glu Ser Ser Lys Pro Gly Pro
2125 2130 2135

tct gct cat gat ctt gct gca caa tta aaa agt agc tta cta gca 6495
Ser Ala His Asp Leu Ala Ala Gln Leu Lys Ser Ser Leu Leu Ala
2140 2145 2150

gaa ata gga ctt act gaa agt gaa ggg cca cct ctc aca tct ttc 6540
Glu Ile Gly Leu Thr Glu Ser Glu Gly Pro Pro Leu Thr Ser Phe
2155 2160 2165

agg cca cag tgt agc ttt atg gga atg gtt att tcc cat gat atg 6585
Arg Pro Gln Cys Ser Phe Met Gly Met Val Ile Ser His Asp Met
2170 2175 2180

ctg cta gga cgt tgg cgc ctt tct tta gaa ctg ttc ggc agg gta 6630
Leu Leu Gly Arg Trp Arg Leu Ser Leu Glu Leu Phe Gly Arg Val
2185 2190 2195

ttc atg gaa gat gtt gga gca gaa cct gga tca atc cta act gaa 6675
Phe Met Glu Asp Val Gly Ala Glu Pro Gly Ser Ile Leu Thr Glu
2200 2205 2210

ttg ggt ggt ttt gag gta aaa gaa tca aaa ttc cgc aga gaa atg 6720
Leu Gly Gly Phe Glu Val Lys Glu Ser Lys Phe Arg Arg Glu Met
2215 2220 2225

gaa aaa ctg aga aac cag cag tca aga gat ttg tca cta gag gtt 6765
Glu Lys Leu Arg Asn Gln Gln Ser Arg Asp Leu Ser Leu Glu Val
2230 2235 2240

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Asp Arg Asp Arg Asp Leu Leu Ile Gln Gln Thr Met Arg Gln Leu
2245 2250 2255

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Asn Asn His Phe Gly Arg Arg Cys Ala Thr Thr Pro Met Ala Val
2260 2265 2270

cac aga gta aaa gtc aca ttt aag gat gag cca gga gag ggc agt 6900
His Arg Val Lys Val Thr Phe Lys Asp Glu Pro Gly Glu Gly Ser
2275 2280 2285

ggt gta gca cga agt ttt tat aca gcc att gca caa gca ttt tta 6945
Gly Val Ala Arg Ser Phe Tyr Thr Ala Ile Ala Gln Ala Phe Leu
2290 2295 2300

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tca  aat gaa aaa ttg cca  aat cta gag tgt atc  caa aat gcc aac     6990
Ser  Asn Glu Lys Leu Pro  Asn Leu Glu Cys Ile  Gln Asn Ala Asn
2305                2310                2315

aaa  ggc acc cac aca agt  tta atg cag aga tta  agg aac cga gga     7035
Lys  Gly Thr His Thr Ser  Leu Met Gln Arg Leu  Arg Asn Arg Gly
2320                2325                2330

gag  aga gac cgg gaa agg  gag aga gaa agg gaa  atg agg agg agt     7080
Glu  Arg Asp Arg Glu Arg  Glu Arg Glu Arg Glu  Met Arg Arg Ser
2335                2340                2345

agt  ggt ttg cga gca ggt  tct cgg agg gac cgg  gat aga gac ttt     7125
Ser  Gly Leu Arg Ala Gly  Ser Arg Arg Asp Arg  Asp Arg Asp Phe
2350                2355                2360

aga  aga cag ctt tcc atc  gac act agg ccc ttt  aga cca gcc tct     7170
Arg  Arg Gln Leu Ser Ile  Asp Thr Arg Pro Phe  Arg Pro Ala Ser
2365                2370                2375

gaa  ggg aat cct agc gat  gat cct gag cct ttg  cca gca cat cgg     7215
Glu  Gly Asn Pro Ser Asp  Asp Pro Glu Pro Leu  Pro Ala His Arg
2380                2385                2390

cag  gca ctt gga gag agg  ctt tat cct cgt gta  caa gca atg caa     7260
Gln  Ala Leu Gly Glu Arg  Leu Tyr Pro Arg Val  Gln Ala Met Gln
2395                2400                2405

cca  gca ttt gca agt aaa  atc act ggc atg ttg  ttg gaa tta tcc     7305
Pro  Ala Phe Ala Ser Lys  Ile Thr Gly Met Leu  Leu Glu Leu Ser
2410                2415                2420

cca  gct cag ctg ctt ctc  ctt cta gca agt gag  gat tct ctg aga     7350
Pro  Ala Gln Leu Leu Leu  Leu Leu Ala Ser Glu  Asp Ser Leu Arg
2425                2430                2435

gca  aga gtg gat gag gcc  atg gaa ctc att att  gca cat gga cgg     7395
Ala  Arg Val Asp Glu Ala  Met Glu Leu Ile Ile  Ala His Gly Arg
2440                2445                2450

gaa  aat gga gct gat agt  atc ctg gat ctt gga  tta gta gac tcc     7440
Glu  Asn Gly Ala Asp Ser  Ile Leu Asp Leu Gly  Leu Val Asp Ser
2455                2460                2465

tca  gaa aag gta cag cag  gaa aac cga aag cgc  cat ggc tct agt     7485
Ser  Glu Lys Val Gln Gln  Glu Asn Arg Lys Arg  His Gly Ser Ser
2470                2475                2480

cga  agt gta gta gat atg  gat tta gat gat aca  gat gat ggt gat     7530
Arg  Ser Val Val Asp Met  Asp Leu Asp Asp Thr  Asp Asp Gly Asp
2485                2490                2495

gac  aat gcc cct ttg ttt  tac caa cct ggg aaa  aga gga ttt tat     7575
Asp  Asn Ala Pro Leu Phe  Tyr Gln Pro Gly Lys  Arg Gly Phe Tyr
2500                2505                2510

act  cca agg cct ggc aag  aac aca gaa gca agg  ttg aat tgt ttc     7620
Thr  Pro Arg Pro Gly Lys  Asn Thr Glu Ala Arg  Leu Asn Cys Phe
2515                2520                2525

aga  aac att ggc agg att  ctt gga cta tgt ctg  tta cag aat gaa     7665
Arg  Asn Ile Gly Arg Ile  Leu Gly Leu Cys Leu  Leu Gln Asn Glu
2530                2535                2540

ctc  tgt cct atc aca ttg  aat aga cat gta att  aaa gta ttg ctt     7710
Leu  Cys Pro Ile Thr Leu  Asn Arg His Val Ile  Lys Val Leu Leu
2545                2550                2555
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Gly  Arg Lys Val Asn Trp  His Asp Phe Ala Phe  Phe Asp Pro Val
2560                 2565                 2570

atg  tat gag agt ttg cgg  caa cta atc ctc gcg  tct cag agt tca      7800
Met  Tyr Glu Ser Leu Arg  Gln Leu Ile Leu Ala  Ser Gln Ser Ser
2575                 2580                 2585

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Asp  Ala Asp Ala Val Phe  Ser Ala Met Asp Leu  Ala Phe Ala Ile
2590                 2595                 2600

gac  ctg tgt aaa gaa gaa  ggt gga gga cag gtt  gaa ctc att cct      7890
Asp  Leu Cys Lys Glu Glu  Gly Gly Gly Gln Val  Glu Leu Ile Pro
2605                 2610                 2615

aat  ggt gta aat ata cca  gtc act cca cag aat  gta tat gag tat      7935
Asn  Gly Val Asn Ile Pro  Val Thr Pro Gln Asn  Val Tyr Glu Tyr
2620                 2625                 2630

gtg  cgg aaa tac gca gaa  cac aga atg ttg gta  gtt gca gaa cag      7980
Val  Arg Lys Tyr Ala Glu  His Arg Met Leu Val  Val Ala Glu Gln
2635                 2640                 2645

ccc  tta cat gca atg agg  aaa ggt cta cta gat  gtg ctt cca aaa      8025
Pro  Leu His Ala Met Arg  Lys Gly Leu Leu Asp  Val Leu Pro Lys
2650                 2655                 2660

aat  tca tta gaa gat tta  acg gca gaa gat ttt  agg ctt ttg gta      8070
Asn  Ser Leu Glu Asp Leu  Thr Ala Glu Asp Phe  Arg Leu Leu Val
2665                 2670                 2675

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Asn  Gly Cys Gly Glu Val  Asn Val Gln Met Leu  Ile Ser Phe Thr
2680                 2685                 2690

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Ser  Phe Asn Asp Glu Ser  Gly Glu Asn Ala Glu  Lys Leu Leu Gln
2695                 2700                 2705

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Phe  Lys Arg Trp Phe Trp  Ser Ile Val Glu Lys  Met Ser Met Thr
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gaa  cga caa gat ctt gtt  tac ttt tgg aca tca  agc cca tca ctg      8250
Glu  Arg Gln Asp Leu Val  Tyr Phe Trp Thr Ser  Ser Pro Ser Leu
2725                 2730                 2735

cca  gcc agt gaa gaa gga  ttc cag cct atg ccc  tca atc aca ata      8295
Pro  Ala Ser Glu Glu Gly  Phe Gln Pro Met Pro  Ser Ile Thr Ile
2740                 2745                 2750

aga  cca cca gat gac caa  cat ctt cct act gca  aat act tgc att      8340
Arg  Pro Pro Asp Asp Gln  His Leu Pro Thr Ala  Asn Thr Cys Ile
2755                 2760                 2765

tct  cga ctt tac gtc cca  ctc tat tcc tct aaa  cag att ctc aaa      8385
Ser  Arg Leu Tyr Val Pro  Leu Tyr Ser Ser Lys  Gln Ile Leu Lys
2770                 2775                 2780

cag  aaa ttg tta ctc gcc  att aag acc aag aat  ttt ggt ttt gtg      8430
Gln  Lys Leu Leu Leu Ala  Ile Lys Thr Lys Asn  Phe Gly Phe Val
2785                 2790                 2795

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<400> 64

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Asn Leu Asn Ser His Pro Pro Leu Asn Val Leu Glu Gln Ala Thr Ile
35 40 45

Lys Gln Cys Val Val Gly Pro Asn His Ala Ala Phe Leu Leu Glu Asp
50 55 60

Gly Arg Val Cys Arg Ile Gly Phe Ser Val Gln Pro Asp Arg Leu Glu
65 70 75 80

Leu Gly Lys Pro Asp Asn Asn Asp Gly Ser Lys Leu Asn Ser Asn Ser
85 90 95

Gly Ala Gly Arg Thr Ser Arg Pro Gly Arg Thr Ser Asp Ser Pro Trp
100 105 110

Phe Leu Ser Gly Ser Glu Thr Leu Gly Arg Leu Ala Gly Asn Thr Leu
115 120 125

Gly Ser Arg Trp Ser Ser Gly Val Gly Gly Ser Gly Gly Gly Ser Ser
130 135 140

Gly Arg Ser Ser Ala Gly Ala Arg Asp Ser Arg Arg Gln Thr Arg Val
145 150 155 160

Ile Arg Thr Gly Arg Asp Arg Gly Ser Gly Leu Leu Gly Ser Gln Pro
165 170 175

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Gln Pro Val Ile Pro Ala Ser Val Ile Pro Glu Glu Leu Ile Ser Gln
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Ala Gln Val Val Leu Gln Gly Lys Ser Arg Ser Val Ile Ile Arg Glu
        195                 200                 205

Leu Gln Arg Thr Asn Leu Asp Val Asn Leu Ala Val Asn Asn Leu Leu
    210                 215                 220

Ser Arg Asp Asp Glu Asp Gly Asp Asp Gly Asp Asp Thr Ala Ser Glu
225                 230                 235                 240

Ser Tyr Leu Pro Gly Glu Asp Leu Met Ser Leu Leu Asp Ala Asp Ile
                245                 250                 255

His Ser Ala His Pro Ser Val Ile Ile Asp Ala Asp Ala Met Phe Ser
            260                 265                 270

Glu Asp Ile Ser Tyr Phe Gly Tyr Pro Ser Phe Arg Arg Ser Ser Leu
        275                 280                 285

Ser Arg Leu Gly Ser Ser Arg Val Leu Leu Leu Pro Leu Glu Arg Asp
    290                 295                 300

Ser Glu Leu Leu Arg Glu Arg Glu Ser Val Leu Arg Leu Arg Glu Arg
305                 310                 315                 320

Arg Trp Leu Asp Gly Ala Ser Phe Asp Asn Glu Arg Gly Ser Thr Ser
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Lys Glu Gly Glu Pro Asn Leu Asp Lys Lys Asn Thr Pro Val Gln Ser
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Pro Val Ser Leu Gly Glu Asp Leu Gln Trp Trp Pro Asp Lys Asp Gly
        355                 360                 365

Thr Lys Phe Ile Cys Ile Gly Ala Leu Tyr Ser Glu Leu Leu Ala Val
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Ser Ser Lys Gly Glu Leu Tyr Gln Trp Lys Trp Ser Glu Ser Glu Pro
385                 390                 395                 400

Tyr Arg Asn Ala Gln Asn Pro Ser Leu His His Pro Arg Ala Thr Phe
                405                 410                 415

Leu Gly Leu Thr Asn Glu Lys Ile Val Leu Leu Ser Ala Asn Ser Ile
            420                 425                 430

Arg Ala Thr Val Ala Thr Glu Asn Asn Lys Val Ala Thr Trp Val Asp
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Glu Thr Leu Ser Ser Val Ala Ser Lys Leu Glu His Thr Ala Gln Thr
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850 855 860

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Cys Cys Phe Arg Asn Asn Asp His Pro Glu Ile Thr Tyr Arg Leu Arg
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Lys Pro Met Arg Phe Val Thr Arg Phe Ile Asp Leu Asp Gly Leu Ser
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cga ata cat act tct ctc att ggc tgt ata aag gcg tta atg aac aac      698
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Ser Gln Gly Arg Ala His Val Leu Ala His Ser Glu Ser Ile Asn Val
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Ile Ala Gln Ser Leu Ser Thr Glu Asn Ile Lys Thr Lys Val Ala Val
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Leu Glu Ile Leu Gly Ala Val Cys Leu Val Pro Gly Gly His Lys Lys
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gtt ctg cag gcc atg ctg cac tac cag aag tat gcc agc gaa agg acc      890
Val Leu Gln Ala Met Leu His Tyr Gln Lys Tyr Ala Ser Glu Arg Thr
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cgc ttt cag aca tta att aac gac ttg gat aaa agc act ggg cgg tat      938
Arg Phe Gln Thr Leu Ile Asn Asp Leu Asp Lys Ser Thr Gly Arg Tyr
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cga gat gaa gtg agt ctc aag act gcc atc atg tcc ttc att aat gca      986
Arg Asp Glu Val Ser Leu Lys Thr Ala Ile Met Ser Phe Ile Asn Ala
            275                 280                 285

gtg ctc agc caa ggt gca gga gtg gag agt ttg gac ttt aga ctt cat     1034
Val Leu Ser Gln Gly Ala Gly Val Glu Ser Leu Asp Phe Arg Leu His
        290                 295                 300

ctt cgc tat gaa ttt ctg atg tta gga att caa cct gta ata gat aaa     1082
Leu Arg Tyr Glu Phe Leu Met Leu Gly Ile Gln Pro Val Ile Asp Lys
    305                 310                 315

tta agg gaa cac gaa aat tca aca tta gat agg cat tta gac ttt ttt     1130
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320                 325                 330                 335

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Leu Val His Ile Asp Thr Lys Ser Ala Thr Gln Met Phe Glu Leu Thr
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Arg Lys Arg Leu Thr His Ser Glu Ala Tyr Pro His Phe Met Ser Ile
        370                 375                 380

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400                 405                 410                 415

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Ile Lys Asn Val Val Arg Met Leu Val Asn Glu Asn Glu Val Lys Gln
            435                 440                 445

tgg aaa gaa caa gcg gaa aaa atg aga aaa gag cac aat gag cta caa      1514
Trp Lys Glu Gln Ala Glu Lys Met Arg Lys Glu His Asn Glu Leu Gln
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cag aaa ctg gaa aag aaa gaa cga gaa tgt gat gct aag act caa gag      1562
Gln Lys Leu Glu Lys Lys Glu Arg Glu Cys Asp Ala Lys Thr Gln Glu
    465                 470                 475

aag gaa gag atg atg cag acc tta aat aaa atg aaa gag aaa ctt gaa      1610
Lys Glu Glu Met Met Gln Thr Leu Asn Lys Met Lys Glu Lys Leu Glu
480                 485                 490                 495

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Lys Glu Thr Thr Glu His Lys Gln Val Lys Gln Gln Val Ala Asp Leu
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Thr Ala Gln Leu His Glu Leu Ser Arg Arg Ala Val Cys Ala Ser Ile
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cca ggt gga ccc tcg cct gga gca cca gga ggg ccc ttt cct tcc tct      1754
Pro Gly Gly Pro Ser Pro Gly Ala Pro Gly Gly Pro Phe Pro Ser Ser
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gtg cct gga tct ctc ctt cct ccc cca cca ccc cca cct cta cca ggt      1802
Val Pro Gly Ser Leu Leu Pro Pro Pro Pro Pro Pro Pro Leu Pro Gly
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Gly Met Leu Pro Pro Pro Pro Pro Pro Leu Pro Pro Gly Gly Pro Pro
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cct ccc cca ggg cct cct ccc tta ggg gca atc atg cca cct cct ggt      1898
Pro Pro Pro Gly Pro Pro Pro Leu Gly Ala Ile Met Pro Pro Pro Gly
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gct cca atg ggc cta gca ctg aag aag aaa agc att cct cag ccc aca      1946
Ala Pro Met Gly Leu Ala Leu Lys Lys Lys Ser Ile Pro Gln Pro Thr
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aat gcc ctg aaa tcc ttc aac tgg tct aaa ctg ccc gag aac aaa ctg      1994
Asn Ala Leu Lys Ser Phe Asn Trp Ser Lys Leu Pro Glu Asn Lys Leu
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gaa gga aca gta tgg acc gaa att gat gat aca aaa gtc ttc aaa att      2042
Glu Gly Thr Val Trp Thr Glu Ile Asp Asp Thr Lys Val Phe Lys Ile
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cta gat ctt gaa gac ctg gaa aga acc ttc tct gcc tat caa aga cag      2090
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aaa tta tcc aat gac gaa atc aaa cgg gca att cta aca atg gac gaa      2282
Lys Leu Ser Asn Asp Glu Ile Lys Arg Ala Ile Leu Thr Met Asp Glu
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Asp Arg Met Ala Lys Ala Asp Arg Phe Leu Phe Glu Met Ser Arg Ile
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Asn His Tyr Gln Gln Arg Leu Gln Ser Leu Tyr Phe Lys Lys Lys Phe
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gca gag cgt gtg gca gaa gtg aaa cct aaa gtg gaa gca att cgt tct      2522
Ala Glu Arg Val Ala Glu Val Lys Pro Lys Val Glu Ala Ile Arg Ser
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gtg gtt ttg gca ttt gga aat tat atg aat aaa ggt caa aga ggg aat      2618
Val Val Leu Ala Phe Gly Asn Tyr Met Asn Lys Gly Gln Arg Gly Asn
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gca tat gga ttc aag ata tct agc cta aac aaa att gct gac aca aaa      2666
Ala Tyr Gly Phe Lys Ile Ser Ser Leu Asn Lys Ile Ala Asp Thr Lys
            835                 840                 845

tcc agc atc gac aaa aac att acc ctt ttg cac tat ctc atc act att      2714
Ser Ser Ile Asp Lys Asn Ile Thr Leu Leu His Tyr Leu Ile Thr Ile
        850                 855                 860

gtg gaa aat aag tac ccc agt gtt ctc aat cta aat gaa gaa ttg cga      2762
Val Glu Asn Lys Tyr Pro Ser Val Leu Asn Leu Asn Glu Glu Leu Arg
    865                 870                 875

gat att cct caa gct gcg aaa gta aac atg act gag ctg gac aaa gaa      2810
Asp Ile Pro Gln Ala Ala Lys Val Asn Met Thr Glu Leu Asp Lys Glu
880                 885                 890                 895

ata agt acc ttg aga agt ggc ttg aaa gca gta gag aca gag ctg gaa      2858
Ile Ser Thr Leu Arg Ser Gly Leu Lys Ala Val Glu Thr Glu Leu Glu
                900                 905                 910

tat cag aag tct cag ccc cca cag ccc gga gat aag ttt gtg tct gtt      2906
Tyr Gln Lys Ser Gln Pro Pro Gln Pro Gly Asp Lys Phe Val Ser Val
            915                 920                 925

gtc agc cag ttc atc aca gta gcc agc ttc agc ttc tct gat gtt gaa      2954
Val Ser Gln Phe Ile Thr Val Ala Ser Phe Ser Phe Ser Asp Val Glu
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930 935 940

gac ctt cta gca gaa gct aaa gac ctg ttt act aaa gca gtg aag cac 3002
Asp Leu Leu Ala Glu Ala Lys Asp Leu Phe Thr Lys Ala Val Lys His
945 950 955

ttt ggg gaa gag gct ggc aaa ata caa cca gat gag ttc ttt ggc att 3050
Phe Gly Glu Glu Ala Gly Lys Ile Gln Pro Asp Glu Phe Phe Gly Ile
960 965 970 975

ttt gat caa ttt ctt caa gct gtg tca gaa gcc aaa caa gaa aac gaa 3098
Phe Asp Gln Phe Leu Gln Ala Val Ser Glu Ala Lys Gln Glu Asn Glu
980 985 990

aat atg aga aag aaa aag gag gaa gaa gaa cgt cga gct cgc atg gaa 3146
Asn Met Arg Lys Lys Lys Glu Glu Glu Glu Arg Arg Ala Arg Met Glu
995 1000 1005

gct cag ctc aaa gaa caa cgt gaa agg gaa cgt aaa atg aga aaa 3191
Ala Gln Leu Lys Glu Gln Arg Glu Arg Glu Arg Lys Met Arg Lys
1010 1015 1020

gct aaa gag aat agt gaa gaa agc gga gag ttt gat gac ctt gtt 3236
Ala Lys Glu Asn Ser Glu Glu Ser Gly Glu Phe Asp Asp Leu Val
1025 1030 1035

tca gct tta cgc tca gga gaa gtg ttt gac aaa gac ctt tct aaa 3281
Ser Ala Leu Arg Ser Gly Glu Val Phe Asp Lys Asp Leu Ser Lys
1040 1045 1050

ttg aaa cgg aat cgc aaa cgt att acc aac cag atg act gac agc 3326
Leu Lys Arg Asn Arg Lys Arg Ile Thr Asn Gln Met Thr Asp Ser
1055 1060 1065

agc aga gag aga cca atc aca aaa ctt aat ttc taattttcca 3369
Ser Arg Glu Arg Pro Ile Thr Lys Leu Asn Phe
1070 1075

tgaatacttt tttttagaaa gctcattagc agccctctaa agtgactaga acgtttcatt 3429

acactgcctt gcaatccaaa cagtggcaat tttttccttc atctgtgagt gaatgtgtga 3489

acgtgtgtat gtaaatgtat gtgtgtatat attaaaaaat gtatatagat gtctgagtgt 3549

tgtctggaga cctatacgta tggttaaaaa gatttatgtt aatgtatgtg ctccaaaacc 3609

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gctttgaatt tctgacattg gtgtggggat acagtctgta aatgtttatt gagaacatct 3969

tgcacacaat ttgaattatg tagaatgtca atcaagtttt tgtatattta aaagttggac 4029

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cagatttttg gaaaaaaaca ctatataaat gcaatccatg cttttttttaa agaacaacat 4149

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<212> PRT

<213> NM_014992 DAAM1

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            20                  25                  30

Asp Ser Asn Phe Ala Leu Gln Thr Met Glu Pro Ala Leu Pro Met Pro
        35                  40                  45

Pro Val Glu Glu Leu Asp Val Met Phe Ser Glu Leu Val Asp Glu Leu
    50                  55                  60

Asp Leu Thr Asp Lys His Arg Glu Ala Met Phe Ala Leu Pro Ala Glu
65                  70                  75                  80

Lys Lys Trp Gln Ile Tyr Cys Ser Lys Lys Lys Asp Gln Glu Glu Asn
                85                  90                  95

Lys Gly Ala Thr Ser Trp Pro Glu Phe Tyr Ile Asp Gln Leu Asn Ser
            100                 105                 110

Met Ala Ala Arg Lys Ser Leu Leu Ala Leu Glu Lys Glu Glu Glu Glu
        115                 120                 125

Glu Arg Ser Lys Thr Ile Glu Ser Leu Lys Thr Ala Leu Arg Thr Lys
    130                 135                 140

Pro Met Arg Phe Val Thr Arg Phe Ile Asp Leu Asp Gly Leu Ser Cys
145                 150                 155                 160

Ile Leu Asn Phe Leu Lys Thr Met Asp Tyr Glu Thr Ser Glu Ser Arg
                165                 170                 175

Ile His Thr Ser Leu Ile Gly Cys Ile Lys Ala Leu Met Asn Asn Ser
            180                 185                 190

Gln Gly Arg Ala His Val Leu Ala His Ser Glu Ser Ile Asn Val Ile
        195                 200                 205

Ala Gln Ser Leu Ser Thr Glu Asn Ile Lys Thr Lys Val Ala Val Leu
    210                 215                 220
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Glu Ile Leu Gly Ala Val Cys Leu Val Pro Gly Gly His Lys Lys Val
225                 230                 235                 240

Leu Gln Ala Met Leu His Tyr Gln Lys Tyr Ala Ser Glu Arg Thr Arg
                245                 250                 255

Phe Gln Thr Leu Ile Asn Asp Leu Asp Lys Ser Thr Gly Arg Tyr Arg
            260                 265                 270

Asp Glu Val Ser Leu Lys Thr Ala Ile Met Ser Phe Ile Asn Ala Val
        275                 280                 285

Leu Ser Gln Gly Ala Gly Val Glu Ser Leu Asp Phe Arg Leu His Leu
    290                 295                 300

Arg Tyr Glu Phe Leu Met Leu Gly Ile Gln Pro Val Ile Asp Lys Leu
305                 310                 315                 320

Arg Glu His Glu Asn Ser Thr Leu Asp Arg His Leu Asp Phe Phe Glu
                325                 330                 335

Met Leu Arg Asn Glu Asp Glu Leu Glu Phe Ala Lys Arg Phe Glu Leu
            340                 345                 350

Val His Ile Asp Thr Lys Ser Ala Thr Gln Met Phe Glu Leu Thr Arg
        355                 360                 365

Lys Arg Leu Thr His Ser Glu Ala Tyr Pro His Phe Met Ser Ile Leu
    370                 375                 380

His His Cys Leu Gln Met Pro Tyr Lys Arg Ser Gly Asn Thr Val Gln
385                 390                 395                 400

Tyr Trp Leu Leu Leu Asp Arg Ile Ile Gln Gln Ile Val Ile Gln Asn
                405                 410                 415

Asp Lys Gly Gln Asp Pro Asp Ser Thr Pro Leu Glu Asn Phe Asn Ile
            420                 425                 430

Lys Asn Val Val Arg Met Leu Val Asn Glu Asn Glu Val Lys Gln Trp
        435                 440                 445

Lys Glu Gln Ala Glu Lys Met Arg Lys Glu His Asn Glu Leu Gln Gln
    450                 455                 460

Lys Leu Glu Lys Lys Glu Arg Glu Cys Asp Ala Lys Thr Gln Glu Lys
465                 470                 475                 480

Glu Glu Met Met Gln Thr Leu Asn Lys Met Lys Glu Lys Leu Glu Lys
                485                 490                 495
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Glu Thr Thr Glu His Lys Gln Val Lys Gln Gln Val Ala Asp Leu Thr
500 505 510

Ala Gln Leu His Glu Leu Ser Arg Arg Ala Val Cys Ala Ser Ile Pro
515 520 525

Gly Gly Pro Ser Pro Gly Ala Pro Gly Gly Pro Phe Pro Ser Ser Val
530 535 540

Pro Gly Ser Leu Leu Pro Pro Pro Pro Pro Pro Pro Leu Pro Gly Gly
545 550 555 560

Met Leu Pro Pro Pro Pro Pro Pro Leu Pro Pro Gly Gly Pro Pro Pro
565 570 575

Pro Pro Gly Pro Pro Pro Leu Gly Ala Ile Met Pro Pro Pro Gly Ala
580 585 590

Pro Met Gly Leu Ala Leu Lys Lys Lys Ser Ile Pro Gln Pro Thr Asn
595 600 605

Ala Leu Lys Ser Phe Asn Trp Ser Lys Leu Pro Glu Asn Lys Leu Glu
610 615 620

Gly Thr Val Trp Thr Glu Ile Asp Asp Thr Lys Val Phe Lys Ile Leu
625 630 635 640

Asp Leu Glu Asp Leu Glu Arg Thr Phe Ser Ala Tyr Gln Arg Gln Gln
645 650 655

Asp Phe Phe Val Asn Ser Asn Ser Lys Gln Lys Glu Ala Asp Ala Ile
660 665 670

Asp Asp Thr Leu Ser Ser Lys Leu Lys Val Lys Glu Leu Ser Val Ile
675 680 685

Asp Gly Arg Arg Ala Gln Asn Cys Asn Ile Leu Leu Ser Arg Leu Lys
690 695 700

Leu Ser Asn Asp Glu Ile Lys Arg Ala Ile Leu Thr Met Asp Glu Gln
705 710 715 720

Glu Asp Leu Pro Lys Asp Met Leu Glu Gln Leu Leu Lys Phe Val Pro
725 730 735

Glu Lys Ser Asp Ile Asp Leu Leu Glu Glu His Lys His Glu Leu Asp
740 745 750

Arg Met Ala Lys Ala Asp Arg Phe Leu Phe Glu Met Ser Arg Ile Asn

755 760 765

His Tyr Gln Gln Arg Leu Gln Ser Leu Tyr Phe Lys Lys Lys Phe Ala
770 775 780

Glu Arg Val Ala Glu Val Lys Pro Lys Val Glu Ala Ile Arg Ser Gly
785 790 795 800

Ser Glu Glu Val Phe Arg Ser Gly Ala Leu Lys Gln Leu Leu Glu Val
805 810 815

Val Leu Ala Phe Gly Asn Tyr Met Asn Lys Gly Gln Arg Gly Asn Ala
820 825 830

Tyr Gly Phe Lys Ile Ser Ser Leu Asn Lys Ile Ala Asp Thr Lys Ser
835 840 845

Ser Ile Asp Lys Asn Ile Thr Leu Leu His Tyr Leu Ile Thr Ile Val
850 855 860

Glu Asn Lys Tyr Pro Ser Val Leu Asn Leu Asn Glu Glu Leu Arg Asp
865 870 875 880

Ile Pro Gln Ala Ala Lys Val Asn Met Thr Glu Leu Asp Lys Glu Ile
885 890 895

Ser Thr Leu Arg Ser Gly Leu Lys Ala Val Glu Thr Glu Leu Glu Tyr
900 905 910

Gln Lys Ser Gln Pro Pro Gln Pro Gly Asp Lys Phe Val Ser Val Val
915 920 925

Ser Gln Phe Ile Thr Val Ala Ser Phe Ser Phe Ser Asp Val Glu Asp
930 935 940

Leu Leu Ala Glu Ala Lys Asp Leu Phe Thr Lys Ala Val Lys His Phe
945 950 955 960

Gly Glu Glu Ala Gly Lys Ile Gln Pro Asp Glu Phe Phe Gly Ile Phe
965 970 975

Asp Gln Phe Leu Gln Ala Val Ser Glu Ala Lys Gln Glu Asn Glu Asn
980 985 990

Met Arg Lys Lys Lys Glu Glu Glu Glu Arg Arg Ala Arg Met Glu Ala
995 1000 1005

Gln Leu Lys Glu Gln Arg Glu Arg Glu Arg Lys Met Arg Lys Ala
1010 1015 1020

Lys Glu Asn Ser Glu Glu Ser Gly Glu Phe Asp Asp Leu Val Ser

1025 1030 1035

Ala Leu Arg Ser Gly Glu Val Phe Asp Lys Asp Leu Ser Lys Leu
1040 1045 1050

Lys Arg Asn Arg Lys Arg Ile Thr Asn Gln Met Thr Asp Ser Ser
1055 1060 1065

Arg Glu Arg Pro Ile Thr Lys Leu Asn Phe
1070 1075

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<211> 1096

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<222> (1)..(765)

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gtg atg agc ccc tgt gga ggt gaa gac att gtg gct gac cac gtt gcc 96
Val Met Ser Pro Cys Gly Gly Glu Asp Ile Val Ala Asp His Val Ala
20 25 30

tct tgt ggt gta aac ttg tac cag ttt tac ggt ccc tct ggc cag tac 144
Ser Cys Gly Val Asn Leu Tyr Gln Phe Tyr Gly Pro Ser Gly Gln Tyr
35 40 45

acc cat gaa ttt gat gga gat gag cag ttc tac gtg gac ctg gag agg 192
Thr His Glu Phe Asp Gly Asp Glu Gln Phe Tyr Val Asp Leu Glu Arg
50 55 60

aag gag act gcc tgg cgg tgg cct gag ttc agc aaa ttt gga ggt ttt 240
Lys Glu Thr Ala Trp Arg Trp Pro Glu Phe Ser Lys Phe Gly Gly Phe
65 70 75 80

gac ccg cag ggt gca ctg aga aac atg gct gtg gca aaa cac aac ttg 288
Asp Pro Gln Gly Ala Leu Arg Asn Met Ala Val Ala Lys His Asn Leu
85 90 95

aac atc atg att aaa cgc tac aac tct acc gct gct acc aat gag gtt 336
Asn Ile Met Ile Lys Arg Tyr Asn Ser Thr Ala Ala Thr Asn Glu Val
100 105 110

cct gag gtc aca gtg ttt tcc aag tct ccc gtg aca ctg ggt cag ccc 384
Pro Glu Val Thr Val Phe Ser Lys Ser Pro Val Thr Leu Gly Gln Pro
115 120 125

aac acc ctc att tgt ctt gtg gac aac atc ttt cct cct gtg gtc aac 432
Asn Thr Leu Ile Cys Leu Val Asp Asn Ile Phe Pro Pro Val Val Asn
130 135 140

atc aca tgg ctg agc aat ggg cag tca gtc aca gaa ggt gtt tct gag 480
Ile Thr Trp Leu Ser Asn Gly Gln Ser Val Thr Glu Gly Val Ser Glu
145 150 155 160

acc agc ttc ctc tcc aag agt gat cat tcc ttc ttc aag atc agt tac 528
Thr Ser Phe Leu Ser Lys Ser Asp His Ser Phe Phe Lys Ile Ser Tyr
165 170 175

ctc acc ttc ctc cct tct gct gat gag att tat gac tgc aag gtg gag 576
Leu Thr Phe Leu Pro Ser Ala Asp Glu Ile Tyr Asp Cys Lys Val Glu
180 185 190

cac tgg ggc ctg gac cag cct ctt ctg aaa cac tgg gag cct gag att 624
His Trp Gly Leu Asp Gln Pro Leu Leu Lys His Trp Glu Pro Glu Ile
195 200 205

cca gcc cct atg tca gag ctc aca gag act gtg gtc tgt gcc ctg ggg 672
Pro Ala Pro Met Ser Glu Leu Thr Glu Thr Val Val Cys Ala Leu Gly
210 215 220

ttg tct gtg ggc ctc atg ggc att gtg gtg ggc act gtc ttc atc atc 720
Leu Ser Val Gly Leu Met Gly Ile Val Val Gly Thr Val Phe Ile Ile
225 230 235 240

caa ggc ctg cgt tca gtt ggt gct tcc aga cac caa ggg cca ttg 765
Gln Gly Leu Arg Ser Val Gly Ala Ser Arg His Gln Gly Pro Leu
245 250 255

tgaatcccat cctggaaggg aaggtgcatc gccatctaca ggagcagaag aatggacttg 825

ctaaatgacc tagcactatt ctctggcccg atttatcata tcccttttct cctccaaata 885

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gcctttacat tctttccctg acctcctgat tttttttttc ttttctcaaa tgttacctac 1005

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<211> 255

<212> PRT

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20 25 30

Ser Cys Gly Val Asn Leu Tyr Gln Phe Tyr Gly Pro Ser Gly Gln Tyr
35 40 45

Thr His Glu Phe Asp Gly Asp Glu Gln Phe Tyr Val Asp Leu Glu Arg
50 55 60

Lys Glu Thr Ala Trp Arg Trp Pro Glu Phe Ser Lys Phe Gly Gly Phe
65 70 75 80

Asp Pro Gln Gly Ala Leu Arg Asn Met Ala Val Ala Lys His Asn Leu
85 90 95

Asn Ile Met Ile Lys Arg Tyr Asn Ser Thr Ala Ala Thr Asn Glu Val
100 105 110

Pro Glu Val Thr Val Phe Ser Lys Ser Pro Val Thr Leu Gly Gln Pro
115 120 125

Asn Thr Leu Ile Cys Leu Val Asp Asn Ile Phe Pro Pro Val Val Asn
130 135 140

Ile Thr Trp Leu Ser Asn Gly Gln Ser Val Thr Glu Gly Val Ser Glu
145 150 155 160

Thr Ser Phe Leu Ser Lys Ser Asp His Ser Phe Phe Lys Ile Ser Tyr
165 170 175

Leu Thr Phe Leu Pro Ser Ala Asp Glu Ile Tyr Asp Cys Lys Val Glu
180 185 190

His Trp Gly Leu Asp Gln Pro Leu Leu Lys His Trp Glu Pro Glu Ile
195 200 205

Pro Ala Pro Met Ser Glu Leu Thr Glu Thr Val Val Cys Ala Leu Gly
210 215 220

Leu Ser Val Gly Leu Met Gly Ile Val Val Gly Thr Val Phe Ile Ile
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Gln Gly Leu Arg Ser Val Gly Ala Ser Arg His Gln Gly Pro Leu
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<210> 69

<211> 2820

<212> DNA

<213> NM_003014 SFRP4, secreted frizzled-related protein 4

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<221> CDS

<222> (238)..(1275)

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aaactctcct gcgccccaga agatttcttc ctcggcgaag ggacagcgaa agatgagggt      180

ggcaggaaga gaaggcgctt tctgtctgcc ggggtcgcag cgcgagaggg cagtgcc         237

atg ttc ctc tcc atc cta gtg gcg ctg tgc ctg tgg ctg cac ctg gcg        285
Met Phe Leu Ser Ile Leu Val Ala Leu Cys Leu Trp Leu His Leu Ala
1               5                   10                  15

ctg ggc gtg cgc ggc gcg ccc tgc gag gcg gtg cgc atc cct atg tgc        333
Leu Gly Val Arg Gly Ala Pro Cys Glu Ala Val Arg Ile Pro Met Cys
            20                  25                  30

cgg cac atg ccc tgg aac atc acg cgg atg ccc aac cac ctg cac cac        381
Arg His Met Pro Trp Asn Ile Thr Arg Met Pro Asn His Leu His His
        35                  40                  45

agc acg cag gag aac gcc atc ctg gcc atc gag cag tac gag gag ctg        429
Ser Thr Gln Glu Asn Ala Ile Leu Ala Ile Glu Gln Tyr Glu Glu Leu
    50                  55                  60

gtg gac gtg aac tgc agc gcc gtg ctg cgc ttc ttc ttc tgt gcc atg        477
Val Asp Val Asn Cys Ser Ala Val Leu Arg Phe Phe Phe Cys Ala Met
65                  70                  75                  80

tac gcg ccc att tgc acc ctg gag ttc ctg cac gac cct atc aag ccg        525
Tyr Ala Pro Ile Cys Thr Leu Glu Phe Leu His Asp Pro Ile Lys Pro
                85                  90                  95

tgc aag tcg gtg tgc caa cgc gcg cgc gac gac tgc gag ccc ctc atg        573
Cys Lys Ser Val Cys Gln Arg Ala Arg Asp Asp Cys Glu Pro Leu Met
            100                 105                 110

aag atg tac aac cac agc tgg ccc gaa agc ctg gcc tgc gac gag ctg        621
Lys Met Tyr Asn His Ser Trp Pro Glu Ser Leu Ala Cys Asp Glu Leu
        115                 120                 125

cct gtc tat gac cgt ggc gtg tgc att tcg cct gaa gcc atc gtc acg        669
Pro Val Tyr Asp Arg Gly Val Cys Ile Ser Pro Glu Ala Ile Val Thr
    130                 135                 140

gac ctc ccg gag gat gtt aag tgg ata gac atc aca cca gac atg atg        717
Asp Leu Pro Glu Asp Val Lys Trp Ile Asp Ile Thr Pro Asp Met Met
145                 150                 155                 160

gta cag gaa agg cct ctt gat gtt gac tgt aaa cgc cta agc ccc gat        765
Val Gln Glu Arg Pro Leu Asp Val Asp Cys Lys Arg Leu Ser Pro Asp
                165                 170                 175

cgg tgc aag tgt aaa aag gtg aag cca act ttg gca acg tat ctc agc        813
Arg Cys Lys Cys Lys Lys Val Lys Pro Thr Leu Ala Thr Tyr Leu Ser
            180                 185                 190

aaa aac tac agc tat gtt att cat gcc aaa ata aaa gct gtg cag agg        861
Lys Asn Tyr Ser Tyr Val Ile His Ala Lys Ile Lys Ala Val Gln Arg
        195                 200                 205

agt ggc tgc aat gag gtc aca acg gtg gtg gat gta aaa gag atc ttc        909
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Ser Gly Cys Asn Glu Val Thr Thr Val Val Asp Val Lys Glu Ile Phe
    210                 215                 220

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Lys Ser Ser Ser Pro Ile Pro Arg Thr Gln Val Pro Leu Ile Thr Asn
225                 230                 235                 240

tct tct tgc cag tgt cca cac atc ctg ccc cat caa gat gtt ctc atc     1005
Ser Ser Cys Gln Cys Pro His Ile Leu Pro His Gln Asp Val Leu Ile
                245                 250                 255

atg tgt tac gag tgg cgt tca agg atg atg ctt ctt gaa aat tgc tta     1053
Met Cys Tyr Glu Trp Arg Ser Arg Met Met Leu Leu Glu Asn Cys Leu
            260                 265                 270

gtt gaa aaa tgg aga gat cag ctt agt aaa aga tcc ata cag tgg gaa     1101
Val Glu Lys Trp Arg Asp Gln Leu Ser Lys Arg Ser Ile Gln Trp Glu
        275                 280                 285

gag agg ctg cag gaa cag cgg aga aca gtt cag gac aag aag aaa aca     1149
Glu Arg Leu Gln Glu Gln Arg Arg Thr Val Gln Asp Lys Lys Lys Thr
    290                 295                 300

gcc ggg cgc acc agt cgt agt aat ccc ccc aaa cca aag gga aag cct     1197
Ala Gly Arg Thr Ser Arg Ser Asn Pro Pro Lys Pro Lys Gly Lys Pro
305                 310                 315                 320

cct gct ccc aaa cca gcc agt ccc aag aag aac att aaa act agg agt     1245
Pro Ala Pro Lys Pro Ala Ser Pro Lys Lys Asn Ile Lys Thr Arg Ser
                325                 330                 335

gcc cag aag aga aca aac ccg aaa aga gtg tgagctaact agtttccaaa       1295
Ala Gln Lys Arg Thr Asn Pro Lys Arg Val
            340                 345

gcggagactt ccgacttcct tacaggatga ggctgggcat tgcctgggac agcctatgta   1355

aggccatgtg ccccttgccc taacaactca ctgcagtgct cttcatagac acatcttgca   1415

gcatttttct taaggctatg cttcagtttt tctttgtaag ccatcacaag ccatagtggt   1475

aggtttgccc tttggtacag aaggtgagtt aaagctggtg gaaaaggctt attgcattgc   1535

attcagagta acctgtgtgc atactctaga agagtaggga aaataatgct tgttacaatt   1595

cgacctaata tgtgcattgt aaaataaatg ccatatttca aacaaaacac gtaatttttt   1655

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gtgatgaaaa tataatgttt ttaagaagga acagtagtgg aatgaatgtt aaaagatctt   1775

tatgtgttta tggtctgcag aaggattttt gtgatgaaag gggatttttt gaaaaattag   1835

agaagtagca tatggaaaat tataatgtgt ttttttacca atgacttcag tttctgtttt   1895

tagctagaaa cttaaaaaca aaaataataa taaagaaaaa taaataaaaa ggagaggcag   1955

acaatgtctg gattcctgtt ttttggttac ctgatttcca tgatcatgat gcttcttgtc   2015

aacaccctct taagcagcac cagaaacagt gagtttgtct gtaccattag gagttaggta   2075

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tacttcccag gacatccacc ctgagaataa tttgacaagc ttaaaaatgg ccttcatgtg   2195

agtgccaaat tttgtttttc ttcatttaaa tattttcttt gcctaaatac atgtgagagg   2255

agttaaatat aaatgtacag agaggaaagt tgagttccac ctctgaaatg agaattactt   2315
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<211> 346

<212> PRT

<213> NM_003014 SFRP4, secreted frizzled-related protein 4

<400> 70

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20 25 30

Arg His Met Pro Trp Asn Ile Thr Arg Met Pro Asn His Leu His His
35 40 45

Ser Thr Gln Glu Asn Ala Ile Leu Ala Ile Glu Gln Tyr Glu Glu Leu
50 55 60

Val Asp Val Asn Cys Ser Ala Val Leu Arg Phe Phe Phe Cys Ala Met
65 70 75 80

Tyr Ala Pro Ile Cys Thr Leu Glu Phe Leu His Asp Pro Ile Lys Pro
85 90 95

Cys Lys Ser Val Cys Gln Arg Ala Arg Asp Asp Cys Glu Pro Leu Met
100 105 110

Lys Met Tyr Asn His Ser Trp Pro Glu Ser Leu Ala Cys Asp Glu Leu
115 120 125

Pro Val Tyr Asp Arg Gly Val Cys Ile Ser Pro Glu Ala Ile Val Thr
130 135 140

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Asp Leu Pro Glu Asp Val Lys Trp Ile Asp Ile Thr Pro Asp Met Met
145                 150                 155                 160

Val Gln Glu Arg Pro Leu Asp Val Asp Cys Lys Arg Leu Ser Pro Asp
                165                 170                 175

Arg Cys Lys Cys Lys Lys Val Lys Pro Thr Leu Ala Thr Tyr Leu Ser
            180                 185                 190

Lys Asn Tyr Ser Tyr Val Ile His Ala Lys Ile Lys Ala Val Gln Arg
        195                 200                 205

Ser Gly Cys Asn Glu Val Thr Thr Val Val Asp Val Lys Glu Ile Phe
    210                 215                 220

Lys Ser Ser Ser Pro Ile Pro Arg Thr Gln Val Pro Leu Ile Thr Asn
225                 230                 235                 240

Ser Ser Cys Gln Cys Pro His Ile Leu Pro His Gln Asp Val Leu Ile
                245                 250                 255

Met Cys Tyr Glu Trp Arg Ser Arg Met Met Leu Leu Glu Asn Cys Leu
            260                 265                 270

Val Glu Lys Trp Arg Asp Gln Leu Ser Lys Arg Ser Ile Gln Trp Glu
        275                 280                 285

Glu Arg Leu Gln Glu Gln Arg Arg Thr Val Gln Asp Lys Lys Lys Thr
    290                 295                 300

Ala Gly Arg Thr Ser Arg Ser Asn Pro Pro Lys Pro Lys Gly Lys Pro
305                 310                 315                 320

Pro Ala Pro Lys Pro Ala Ser Pro Lys Lys Asn Ile Lys Thr Arg Ser
                325                 330                 335

Ala Gln Lys Arg Thr Asn Pro Lys Arg Val
            340                 345
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<210> 71

<211> 1362

<212> DNA

<213> NM_004039 annexin A2

<220>

<221> CDS

<222> (50)..(1066)

<223>

<400> 71
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Met Ser Thr
1

gtt cac gaa atc ctg tgc aag ctc agc ttg gag ggt gat cac tct aca 106
Val His Glu Ile Leu Cys Lys Leu Ser Leu Glu Gly Asp His Ser Thr
5 10 15

ccc cca agt gca tat ggg tct gtc aaa gcc tat act aac ttt gat gct 154
Pro Pro Ser Ala Tyr Gly Ser Val Lys Ala Tyr Thr Asn Phe Asp Ala
20 25 30 35

gag cgg gat gct ttg aac att gaa aca gcc atc aag acc aaa ggt gtg 202
Glu Arg Asp Ala Leu Asn Ile Glu Thr Ala Ile Lys Thr Lys Gly Val
40 45 50

gat gag gtc acc att gtc aac att ttg acc aac cgc agc aat gca cag 250
Asp Glu Val Thr Ile Val Asn Ile Leu Thr Asn Arg Ser Asn Ala Gln
55 60 65

aga cag gat att gcc ttc gcc tac cag aga agg acc aaa aag gaa ctt 298
Arg Gln Asp Ile Ala Phe Ala Tyr Gln Arg Arg Thr Lys Lys Glu Leu
70 75 80

gca tca gca ctg aag tca gcc tta tct ggc cac ctg gag acg gtg att 346
Ala Ser Ala Leu Lys Ser Ala Leu Ser Gly His Leu Glu Thr Val Ile
85 90 95

ttg ggc cta ttg aag aca cct gct cag tat gac gct tct gag cta aaa 394
Leu Gly Leu Leu Lys Thr Pro Ala Gln Tyr Asp Ala Ser Glu Leu Lys
100 105 110 115

gct tcc atg aag ggg ctg gga acc gac gag gac tct ctc att gag atc 442
Ala Ser Met Lys Gly Leu Gly Thr Asp Glu Asp Ser Leu Ile Glu Ile
120 125 130

atc tgc tcc aga acc aac cag gag ctg cag gaa att aac aga gtc tac 490
Ile Cys Ser Arg Thr Asn Gln Glu Leu Gln Glu Ile Asn Arg Val Tyr
135 140 145

aag gaa atg tac aag act gat ctg gag aag gac att att tcg gac aca 538
Lys Glu Met Tyr Lys Thr Asp Leu Glu Lys Asp Ile Ile Ser Asp Thr
150 155 160

tct ggt gac ttc cgc aag ctg atg gtt gcc ctg gca aag ggt aga aga 586
Ser Gly Asp Phe Arg Lys Leu Met Val Ala Leu Ala Lys Gly Arg Arg
165 170 175

gca gag gat ggc tct gtc att gat tat gaa ctg att gac caa gat gct 634
Ala Glu Asp Gly Ser Val Ile Asp Tyr Glu Leu Ile Asp Gln Asp Ala
180 185 190 195

cgg gat ctc tat gac gct gga gtg aag agg aaa gga act gat gtt ccc 682
Arg Asp Leu Tyr Asp Ala Gly Val Lys Arg Lys Gly Thr Asp Val Pro
200 205 210

aag tgg atc agc atc atg acc gag cgg agc gtg ccc cac ctc cag aaa 730
Lys Trp Ile Ser Ile Met Thr Glu Arg Ser Val Pro His Leu Gln Lys
215 220 225

gta ttt gat agg tac aag agt tac agc cct tat gac atg ttg gaa agc 778
Val Phe Asp Arg Tyr Lys Ser Tyr Ser Pro Tyr Asp Met Leu Glu Ser
230 235 240

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atc agg aaa gag gtt aaa gga gac ctg gaa aat gct ttc ctg aac ctg      826
Ile Arg Lys Glu Val Lys Gly Asp Leu Glu Asn Ala Phe Leu Asn Leu
    245                 250                 255

gtt cag tgc att cag aac aag ccc ctg tat ttt gct gat cgg ctg tat      874
Val Gln Cys Ile Gln Asn Lys Pro Leu Tyr Phe Ala Asp Arg Leu Tyr
260                 265                 270                 275

gac tcc atg aag ggc aag ggg acg cga gat aag gtc ctg atc aga atc      922
Asp Ser Met Lys Gly Lys Gly Thr Arg Asp Lys Val Leu Ile Arg Ile
                280                 285                 290

atg gtc tcc cgc agt gaa gtg gac atg ttg aaa att agg tct gaa ttc      970
Met Val Ser Arg Ser Glu Val Asp Met Leu Lys Ile Arg Ser Glu Phe
            295                 300                 305

aag aga aag tac ggc aag tcc ctg tac tat tat atc cag caa gac act     1018
Lys Arg Lys Tyr Gly Lys Ser Leu Tyr Tyr Tyr Ile Gln Gln Asp Thr
        310                 315                 320

aag ggc gac tac cag aaa gcg ctg ctg tac ctg tgt ggt gga gat gac     1066
Lys Gly Asp Tyr Gln Lys Ala Leu Leu Tyr Leu Cys Gly Gly Asp Asp
    325                 330                 335

tgaagcccga cacggcctga gcgtccagaa atggtgctca ccatgcttcc agctaacagg   1126

tctagaaaac cagcttgcga ataacagtcc ccgtggccat ccctgtgagg gtgacgttag   1186

cattaccccc aacctcattt tagttgccta agcattgcct ggccttcctg tctagtctct   1246

cctgtaagcc aaagaaatga acattccaag gagttggaag tgaagtctat gatgtgaaac   1306

actttgcctc ctgtgtactg tgtcataaac agatgaataa actgaatttg tacttt       1362
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<210> 72

<211> 339

<212> PRT

<213> NM_004039 annexin A2

<400> 72

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1               5                   10                  15

His Ser Thr Pro Pro Ser Ala Tyr Gly Ser Val Lys Ala Tyr Thr Asn
            20                  25                  30

Phe Asp Ala Glu Arg Asp Ala Leu Asn Ile Glu Thr Ala Ile Lys Thr
        35                  40                  45

Lys Gly Val Asp Glu Val Thr Ile Val Asn Ile Leu Thr Asn Arg Ser
    50                  55                  60

Asn Ala Gln Arg Gln Asp Ile Ala Phe Ala Tyr Gln Arg Arg Thr Lys
65                  70                  75                  80
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Lys Glu Leu Ala Ser Ala Leu Lys Ser Ala Leu Ser Gly His Leu Glu
85 90 95

Thr Val Ile Leu Gly Leu Leu Lys Thr Pro Ala Gln Tyr Asp Ala Ser
100 105 110

Glu Leu Lys Ala Ser Met Lys Gly Leu Gly Thr Asp Glu Asp Ser Leu
115 120 125

Ile Glu Ile Ile Cys Ser Arg Thr Asn Gln Glu Leu Gln Glu Ile Asn
130 135 140

Arg Val Tyr Lys Glu Met Tyr Lys Thr Asp Leu Glu Lys Asp Ile Ile
145 150 155 160

Ser Asp Thr Ser Gly Asp Phe Arg Lys Leu Met Val Ala Leu Ala Lys
165 170 175

Gly Arg Arg Ala Glu Asp Gly Ser Val Ile Asp Tyr Glu Leu Ile Asp
180 185 190

Gln Asp Ala Arg Asp Leu Tyr Asp Ala Gly Val Lys Arg Lys Gly Thr
195 200 205

Asp Val Pro Lys Trp Ile Ser Ile Met Thr Glu Arg Ser Val Pro His
210 215 220

Leu Gln Lys Val Phe Asp Arg Tyr Lys Ser Tyr Ser Pro Tyr Asp Met
225 230 235 240

Leu Glu Ser Ile Arg Lys Glu Val Lys Gly Asp Leu Glu Asn Ala Phe
245 250 255

Leu Asn Leu Val Gln Cys Ile Gln Asn Lys Pro Leu Tyr Phe Ala Asp
260 265 270

Arg Leu Tyr Asp Ser Met Lys Gly Lys Gly Thr Arg Asp Lys Val Leu
275 280 285

Ile Arg Ile Met Val Ser Arg Ser Glu Val Asp Met Leu Lys Ile Arg
290 295 300

Ser Glu Phe Lys Arg Lys Tyr Gly Lys Ser Leu Tyr Tyr Tyr Ile Gln
305 310 315 320

Gln Asp Thr Lys Gly Asp Tyr Gln Lys Ala Leu Leu Tyr Leu Cys Gly
325 330 335

Gly Asp Asp

<210> 73

<211> 850

<212> DNA

<213> NM_003955 SOCS3

<220>

<221> CDS

<222> (107)..(781)

<223>

<400> 73
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gcagctgcag ccgccgccgc gcagatccac gctggctccg tgcgcc atg gtc acc        115
                                                   Met Val Thr
                                                   1

cac agc aag ttt ccc gcc gcc ggg atg agc cgc ccc ctg gac acc agc       163
His Ser Lys Phe Pro Ala Ala Gly Met Ser Arg Pro Leu Asp Thr Ser
    5                   10                  15

ctg cgc ctc aag acc ttc agc tcc aag agc gag tac cag ctg gtg gtg       211
Leu Arg Leu Lys Thr Phe Ser Ser Lys Ser Glu Tyr Gln Leu Val Val
20                  25                  30                  35

aac gca gtg cgc aag ctg cag gag agc ggc ttc tac tgg agc gca gtg       259
Asn Ala Val Arg Lys Leu Gln Glu Ser Gly Phe Tyr Trp Ser Ala Val
                40                  45                  50

acc ggc ggc gag gcg aac ctg ctg ctc agt gcc gag ccc gcc ggc acc       307
Thr Gly Gly Glu Ala Asn Leu Leu Leu Ser Ala Glu Pro Ala Gly Thr
            55                  60                  65

ttt ctg atc cgc gac agc tcg gac cag cgc cac ttc ttc acg ctc agc       355
Phe Leu Ile Arg Asp Ser Ser Asp Gln Arg His Phe Phe Thr Leu Ser
        70                  75                  80

gtc aag acc cag tct ggg acc aag aac ctg cgc atc cag tgt gag ggg       403
Val Lys Thr Gln Ser Gly Thr Lys Asn Leu Arg Ile Gln Cys Glu Gly
    85                  90                  95

ggc agc ttc tct ctg cag agc gat ccc cgg agc acg cag ccc gtg ccc       451
Gly Ser Phe Ser Leu Gln Ser Asp Pro Arg Ser Thr Gln Pro Val Pro
100                 105                 110                 115

cgc ttc gac tgc gtg ctc aag ctg gtg tac cac tac atg ccg ccc cct       499
Arg Phe Asp Cys Val Leu Lys Leu Val Tyr His Tyr Met Pro Pro Pro
                120                 125                 130

gga gcc ccc tcc ttc ccc tcg cca cct act gaa ccc tcc tcc gag gtg       547
Gly Ala Pro Ser Phe Pro Ser Pro Pro Thr Glu Pro Ser Ser Glu Val
            135                 140                 145

ccc gag cag ccg tct gcc cag cca ctc cct ggg agt ccc ccc aga aga       595
Pro Glu Gln Pro Ser Ala Gln Pro Leu Pro Gly Ser Pro Pro Arg Arg
        150                 155                 160

gcc tat tac atc tac tcc ggg ggc gag aag atc ccc ctg gtg ttg agc       643
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Ala Tyr Tyr Ile Tyr Ser Gly Gly Glu Lys Ile Pro Leu Val Leu Ser
    165                 170                 175

cgg ccc ctc tcc tcc aac gtg gcc act ctt cag cat ctc tgt cgg aag      691
Arg Pro Leu Ser Ser Asn Val Ala Thr Leu Gln His Leu Cys Arg Lys
180                 185                 190                 195

acc gtc aac ggc cac ctg gac tcc tat gag aaa gtc acc cag ctg ccg      739
Thr Val Asn Gly His Leu Asp Ser Tyr Glu Lys Val Thr Gln Leu Pro
                200                 205                 210

ggg ccc att cgg gag ttc ctg gac cag tac gat gcc ccg ctt              781
Gly Pro Ile Arg Glu Phe Leu Asp Gln Tyr Asp Ala Pro Leu
            215                 220                 225

taaggggtaa agggcgcaaa gggcatgggt cgggagaggg gacgcaggcc cctctcctcc    841

gtggcacat                                                            850


<210>  74

<211>  225

<212>  PRT

<213>  NM_003955 SOCS3


<400>  74

Met Val Thr His Ser Lys Phe Pro Ala Ala Gly Met Ser Arg Pro Leu
1               5                   10                  15


Asp Thr Ser Leu Arg Leu Lys Thr Phe Ser Ser Lys Ser Glu Tyr Gln
            20                  25                  30


Leu Val Val Asn Ala Val Arg Lys Leu Gln Glu Ser Gly Phe Tyr Trp
        35                  40                  45


Ser Ala Val Thr Gly Gly Glu Ala Asn Leu Leu Leu Ser Ala Glu Pro
    50                  55                  60


Ala Gly Thr Phe Leu Ile Arg Asp Ser Ser Asp Gln Arg His Phe Phe
65                  70                  75                  80


Thr Leu Ser Val Lys Thr Gln Ser Gly Thr Lys Asn Leu Arg Ile Gln
                85                  90                  95


Cys Glu Gly Gly Ser Phe Ser Leu Gln Ser Asp Pro Arg Ser Thr Gln
            100                 105                 110


Pro Val Pro Arg Phe Asp Cys Val Leu Lys Leu Val Tyr His Tyr Met
        115                 120                 125


Pro Pro Pro Gly Ala Pro Ser Phe Pro Ser Pro Pro Thr Glu Pro Ser
    130                 135                 140
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Ser Glu Val Pro Glu Gln Pro Ser Ala Gln Pro Leu Pro Gly Ser Pro
145 150 155 160

Pro Arg Arg Ala Tyr Tyr Ile Tyr Ser Gly Gly Glu Lys Ile Pro Leu
165 170 175

Val Leu Ser Arg Pro Leu Ser Ser Asn Val Ala Thr Leu Gln His Leu
180 185 190

Cys Arg Lys Thr Val Asn Gly His Leu Asp Ser Tyr Glu Lys Val Thr
195 200 205

Gln Leu Pro Gly Pro Ile Arg Glu Phe Leu Asp Gln Tyr Asp Ala Pro
210 215 220

Leu
225

<210> 75

<211> 369

<212> DNA

<213> NM_000331 SAA1, serum amyloid A1

<220>

<221> CDS

<222> (1)..(366)

<223>

<400> 75
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Met Lys Leu Leu Thr Gly Leu Val Phe Cys Ser Leu Val Leu Gly Val
1 5 10 15

agc agc cga agc ttc ttt tcg ttc ctt ggc gag gct ttt gat ggg gct 96
Ser Ser Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala
20 25 30

cgg gac atg tgg aga gcc tac tct gac atg aga gaa gcc aat tac atc 144
Arg Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile
35 40 45

ggc tca gac aaa tac ttc cat gct cgg ggg aac tat gat gct gcc aaa 192
Gly Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys
50 55 60

agg gga cct ggg ggt gtc tgg gct gca gaa gcg atc agc gat gcc aga 240
Arg Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asp Ala Arg
65 70 75 80

gag aat atc cag aga ttc ttt ggc cat ggt gcg gag gac tcg ctg gct 288
Glu Asn Ile Gln Arg Phe Phe Gly His Gly Ala Glu Asp Ser Leu Ala
85 90 95

gat cag gct gcc aat gaa tgg ggc agg agt ggc aaa gac ccc aat cac 336
Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His
100 105 110

ttc cga cct gct ggc ctg cct gag aaa tac tga 369
Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
115 120

<210> 76

<211> 122

<212> PRT

<213> NM_000331 SAA1, serum amyloid A1

<400> 76

Met Lys Leu Leu Thr Gly Leu Val Phe Cys Ser Leu Val Leu Gly Val
1 5 10 15

Ser Ser Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala
20 25 30

Arg Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile
35 40 45

Gly Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys
50 55 60

Arg Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asp Ala Arg
65 70 75 80

Glu Asn Ile Gln Arg Phe Phe Gly His Gly Ala Glu Asp Ser Leu Ala
85 90 95

Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His
100 105 110

Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
115 120

<210> 77

<211> 895

<212> DNA

<213> NM_014059 RGC32

<220>

<221> CDS

<222> (147)..(497)

<223>

<400> 77

gcggccgcgt cgaccggcgc ggctggagcg cagcgccgaa gggactggca gggctgaagt 60

gtgcgggaca gcaagccccc gaatagcccc ggctgccacc tcgcaggacc caaggccacg 120

cgcgccgggc ccagctgagc cgcctc atg aag ccg ccc gcg gag gac ctg tcg 173
Met Lys Pro Pro Ala Glu Asp Leu Ser
1 5

gac gcg ctg tgc gag ttt gac gcg gtg ctg gcc gac ttc gcg tcg ccc 221
Asp Ala Leu Cys Glu Phe Asp Ala Val Leu Ala Asp Phe Ala Ser Pro
10 15 20 25

ttc cac gag cgc cac ttc cac tac gag gag cac ctg gag cgc atg aag 269
Phe His Glu Arg His Phe His Tyr Glu Glu His Leu Glu Arg Met Lys
30 35 40

cgg cgc agc agc gcc agt gtc agc gac agc agc ggc ttc agc gac tcg 317
Arg Arg Ser Ser Ala Ser Val Ser Asp Ser Ser Gly Phe Ser Asp Ser
45 50 55

gag agt gca gat tca ctt tat agg aac agc ttc agc ttc agt gat gaa 365
Glu Ser Ala Asp Ser Leu Tyr Arg Asn Ser Phe Ser Phe Ser Asp Glu
60 65 70

aaa ctg aat tct cca aca gac tct acc cca gct ctt ctc tct gcc act 413
Lys Leu Asn Ser Pro Thr Asp Ser Thr Pro Ala Leu Leu Ser Ala Thr
75 80 85

gtc act cct cag aaa gct aaa tta gga gac aca aaa gag cta gaa gcc 461
Val Thr Pro Gln Lys Ala Lys Leu Gly Asp Thr Lys Glu Leu Glu Ala
90 95 100 105

ttc att gct gat ctt gac aaa act tta gca agt atg tgaaacaaga 507
Phe Ile Ala Asp Leu Asp Lys Thr Leu Ala Ser Met
110 115

agttctgggt cctttcatca taagggagaa gcttcagaaa gttccgagga cctgctaaaa 567

tcagctacta gaatctgctg ccagagggga caaagacgtg cactcaacct tctaccaggc 627

cactctcagg ctcaccttaa aatcagccct tgatcccatt tctgggcaat ttagacagtg 687

aaactgactt tgtttacctg cttgcagcat attagaacag acgatccatg ctaatattgt 747

attttctctt aaaacatagc tttcctgtaa tttaaagtgc ttttatgaaa atatttgtaa 807

ttaattatat atagttggaa atagcagtaa gctttcccat tataatatat ttttgtatac 867

aaataaaatt tgaactgaac ctcgtgcc 895

<210> 78

<211> 117

<212> PRT

<213> NM_014059 RGC32

<400>. 78

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Met Lys Pro Pro Ala Glu Asp Leu Ser Asp Ala Leu Cys Glu Phe Asp
1               5                   10                  15

Ala Val Leu Ala Asp Phe Ala Ser Pro Phe His Glu Arg His Phe His
            20                  25                  30

Tyr Glu Glu His Leu Glu Arg Met Lys Arg Arg Ser Ser Ala Ser Val
        35                  40                  45

Ser Asp Ser Ser Gly Phe Ser Asp Ser Glu Ser Ala Asp Ser Leu Tyr
    50                  55                  60

Arg Asn Ser Phe Ser Phe Ser Asp Glu Lys Leu Asn Ser Pro Thr Asp
65                  70                  75                  80

Ser Thr Pro Ala Leu Leu Ser Ala Thr Val Thr Pro Gln Lys Ala Lys
                85                  90                  95

Leu Gly Asp Thr Lys Glu Leu Glu Ala Phe Ile Ala Asp Leu Asp Lys
            100                 105                 110

Thr Leu Ala Ser Met
        115
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<210> 79

<211> 1564

<212> DNA

<213> NM_018004 FLJ10134

<220>

<221> CDS

<222> (314)..(1138)

<223>

<400> 79

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ccacgtcctc tccttctcgc cacttattat ttattcgttt tcccaaagaa gcgactaggg     120

acccaagttt aaaaattcct ccccccactc aatgcgagac gtggccagat cccatccaac     180

acacggttta attttcatgg ggctctggga tcaaaagaac agaaacagca acaacaaaag     240

cccagccgct gtctgatttt aagctggcaa agtgggaaaa ataaagtgtt gagtaaacag     300

accaagttgg atc atg ggg aat ttc aga ggt cat gcc ctc cct gga acc        349
               Met Gly Asn Phe Arg Gly His Ala Leu Pro Gly Thr
               1               5                   10
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ttc ttt ttt att att ggt ctt tgg tgg tgt aca aag agt att ctg aag      397
Phe Phe Phe Ile Ile Gly Leu Trp Trp Cys Thr Lys Ser Ile Leu Lys
        15                  20                  25

tat atc tgc aaa aag caa aag cga acc tgc tat ctt ggt tcc aaa aca      445
Tyr Ile Cys Lys Lys Gln Lys Arg Thr Cys Tyr Leu Gly Ser Lys Thr
    30                  35                  40

tta ttc tat cga ttg gaa att ttg gag gga att aca ata gtt ggc atg      493
Leu Phe Tyr Arg Leu Glu Ile Leu Glu Gly Ile Thr Ile Val Gly Met
45                  50                  55                  60

gct tta act ggc atg gct ggg gag cag ttt att cct gga ggg ccc cat      541
Ala Leu Thr Gly Met Ala Gly Glu Gln Phe Ile Pro Gly Gly Pro His
                65                  70                  75

ctg atg tta tat gac tat aaa caa ggt cac tgg aat caa ctc ctg ggc      589
Leu Met Leu Tyr Asp Tyr Lys Gln Gly His Trp Asn Gln Leu Leu Gly
            80                  85                  90

tgg cat cat ttc acc atg tat ttc ttc ttt ggg ctg ttg ggt gtg gca      637
Trp His His Phe Thr Met Tyr Phe Phe Phe Gly Leu Leu Gly Val Ala
        95                  100                 105

gat atc tta tgt ttc acc atc agt tca ctt cct gtg tcc tta acc aag      685
Asp Ile Leu Cys Phe Thr Ile Ser Ser Leu Pro Val Ser Leu Thr Lys
    110                 115                 120

tta atg ttg tca aat gcc tta ttt gtg gag gcc ttt atc ttc tac aac      733
Leu Met Leu Ser Asn Ala Leu Phe Val Glu Ala Phe Ile Phe Tyr Asn
125                 130                 135                 140

cac act cat ggc cgg gaa atg ctg gac atc ttt gtg cac cag ctg ctg      781
His Thr His Gly Arg Glu Met Leu Asp Ile Phe Val His Gln Leu Leu
                145                 150                 155

gtt ttg gtc gtc ttt ctg aca ggc ctc gtt gcc ttc cta gag ttc ctt      829
Val Leu Val Val Phe Leu Thr Gly Leu Val Ala Phe Leu Glu Phe Leu
            160                 165                 170

gtt cgg aac aat gta ctt ctg gag cta ttg cgg tca agt ctc att ctg      877
Val Arg Asn Asn Val Leu Leu Glu Leu Leu Arg Ser Ser Leu Ile Leu
        175                 180                 185

ctt cag ggg agc tgg ttc ttt cag att gga ttt gtc ctg tat ccc ccc      925
Leu Gln Gly Ser Trp Phe Phe Gln Ile Gly Phe Val Leu Tyr Pro Pro
    190                 195                 200

agt gga ggt cct gca tgg gat ctg atg gat cat gaa aat att ttg ttt      973
Ser Gly Gly Pro Ala Trp Asp Leu Met Asp His Glu Asn Ile Leu Phe
205                 210                 215                 220

ctc acc ata tgc ttt tgt tgg cat tat gca gta acc att gtc atc gtt      1021
Leu Thr Ile Cys Phe Cys Trp His Tyr Ala Val Thr Ile Val Ile Val
                225                 230                 235

gga atg aat tat gct ttc att acc tgg ttg gtt aaa tct aga ctt aag      1069
Gly Met Asn Tyr Ala Phe Ile Thr Trp Leu Val Lys Ser Arg Leu Lys
            240                 245                 250

agg ctc tgc tcc tca gaa gtt gga ctt ctg aaa aat gct gaa cga gaa      1117
Arg Leu Cys Ser Ser Glu Val Gly Leu Leu Lys Asn Ala Glu Arg Glu
        255                 260                 265

caa gaa tca gaa gaa gaa atg tgactttgat gagcttccag tttttctaga         1168
Gln Glu Ser Glu Glu Glu Met
    270                 275
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taaacctttt cttttttaca ttgttcttgg ttttgtttct cgatcttttg tttggagaac 1228

agctggctaa ggatgactct aagtgtactg tttgcatttc caatttggtt aaagtatttg 1288

aatttaaata ttttcttttt agctttgaaa atattttggg tgatactttc attttgcaca 1348

tcatgcacat catggtattc aggggctaga gtgatttttt tccagattat ctaaagttgg 1408

atgcccacac tatgaaagaa atatttgttt tatttgcctt atagatatgc tcaaggttac 1468

tgggcttgct actatttgta actccttgac catggaatta tacttgttta tcttgttgct 1528

gcaatgagaa ataaatgaat gtatgtattt tggtgc 1564

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<211> 275

<212> PRT

<213> NM_018004 FLJ10134

<400> 80

Met Gly Asn Phe Arg Gly His Ala Leu Pro Gly Thr Phe Phe Phe Ile
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Ile Gly Leu Trp Trp Cys Thr Lys Ser Ile Leu Lys Tyr Ile Cys Lys
20 25 30

Lys Gln Lys Arg Thr Cys Tyr Leu Gly Ser Lys Thr Leu Phe Tyr Arg
35 40 45

Leu Glu Ile Leu Glu Gly Ile Thr Ile Val Gly Met Ala Leu Thr Gly
50 55 60

Met Ala Gly Glu Gln Phe Ile Pro Gly Gly Pro His Leu Met Leu Tyr
65 70 75 80

Asp Tyr Lys Gln Gly His Trp Asn Gln Leu Leu Gly Trp His His Phe
85 90 95

Thr Met Tyr Phe Phe Phe Gly Leu Leu Gly Val Ala Asp Ile Leu Cys
100 105 110

Phe Thr Ile Ser Ser Leu Pro Val Ser Leu Thr Lys Leu Met Leu Ser
115 120 125

Asn Ala Leu Phe Val Glu Ala Phe Ile Phe Tyr Asn His Thr His Gly
130 135 140

Arg Glu Met Leu Asp Ile Phe Val His Gln Leu Leu Val Leu Val Val
145 150 155 160

Phe Leu Thr Gly Leu Val Ala Phe Leu Glu Phe Leu Val Arg Asn Asn
165 170 175

Val Leu Leu Glu Leu Leu Arg Ser Ser Leu Ile Leu Leu Gln Gly Ser
180 185 190

Trp Phe Phe Gln Ile Gly Phe Val Leu Tyr Pro Pro Ser Gly Gly Pro
195 200 205

Ala Trp Asp Leu Met Asp His Glu Asn Ile Leu Phe Leu Thr Ile Cys
210 215 220

Phe Cys Trp His Tyr Ala Val Thr Ile Val Ile Val Gly Met Asn Tyr
225 230 235 240

Ala Phe Ile Thr Trp Leu Val Lys Ser Arg Leu Lys Arg Leu Cys Ser
245 250 255

Ser Glu Val Gly Leu Leu Lys Asn Ala Glu Arg Glu Gln Glu Ser Glu
260 265 270

Glu Glu Met
275

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Lys Gly Glu Ile Lys Ser Glu Phe Lys Asp Ile Glu Glu Ile Lys Thr
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU03/01166

A.	**CLASSIFICATION OF SUBJECT MATTER**
Int. Cl. 7:	C12Q 1/68, G01N 33/53
According to International Patent Classification (IPC) or to both national classification and IPC	
B.	**FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)
SEE BELOW

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
SEE BELOW

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
DGENE, EMBL, GENBANK: SEQ ID NOS 1-7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 46, 48, 50, 52, 53, 55, 57, 59, 60- 63, 65, 67, 69, 71-75, 77, 79, 81, 83 WPIDS: ovarian, cancer, tumour, detect, diagnose

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Weitzel JN et al (1994) Gynecologic Oncology 55, pages 245-252 "Molecular genetic changes associated with ovarian cancer" and GENBANK ACC M62397 See table 3 and pages 249 and 50 with respect to SEQ ID NOs 3, 4 (MCC)	1-5, 7, 9-12, 16-20, 22, 24-27, 31-43, 62-69
X	DGENE Abstract Accession No ABQ54626 & WO 02 00677 A1 (HUMAN GENOME SCIENCES, INC.) 3 January 2002 See abstract and claim 1, SEQ ID NO 506 (applicant's SEQ ID NO 9)	1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 60-69

[X] Further documents are listed in the continuation of Box C   [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 October 2003	06 NOV 2003

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Telephone No : (02) 6283 2632

C (Continuation 1). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Hough CD et al (2000) Cancer Research 60, 6281-7 "Large-scale serial analysis of gene expression reveals genes differentially expressed in ovarian cancer" See table 3: mal2, claudin 3(relevant to SEQ ID NOs 11, 15)	1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 60-69
PX	WO 02 071928 A2 (MILLENNIUM PHARMACEUTICALS, INC) 19 September 2002 See table 1 pg 20 KIAA0869: pg 19 FLJ22252: pg 21 SLP1, pgs 21, 24, 25 PAX8: pg 18 ANXA2 (applicant's SEQ ID NOs 13, 17, 25, 43 and 71/72) & DGENE Accession No ABS76418 (applicant's SEQ ID NO 17)	1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 45, 47-53, 60-69
PX	WO 02 102235 A2 (EOS BIOTECHNOLOGY, INC) 27 December 2002 See pg 187 KIAA0869: pg 184 claudin 7: pgs 111, 162 and 180 KIAA0101: pg 120 KIAA1481, pgs 152, 174, 184, 202 paired box gene 8: pgs 155, 161 methylene tetrahydrofolate dehydrogenase: pg 176 DD5: pg 125 SOCS3: pg 261 serum amyloid A1 (applicant's SEQ ID NOs 13, 21, 23, 37, 43, 55, 63, 73/74 and 75)	1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 45, 47-53, 60-69
PX	DGENE Abstract Accession No ACA66405 & US 2003/0004102 A1 (ASHKENAZI AJ et al) 2 January 2003 See abstract and claim 2, figure 203 (applicant's SEQ ID NO 19)	1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 60-69
X	Scheurle D et al "Cancer gene discovery using digital differential display" (2000)(online), (retrieved on 16 October 2003) Retrieved from Internet<URL:http://www.fau.edu/cmbb/publications/cancergenes.htm> See "up-regulation of known genes: claudin 7, secreted frizzled rel. pro. 4 (applicant's SEQ ID NOs 21 and 69)	1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 45, 47-53, 60-69
X	DGENE Abstract Accession No AAS56533 & WO 01 70796 A2 (CORIXA CORPORATION) 27 September 2001 See abstract and claim 1, page 165 KIAA0101 (applicant's SEQ ID NO 23)	1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 60-69
X	Medline Abstract 11906548 Shigemasa K et al (2001) Int J Gynecol Cancer 11(6), 454-61 "Expression of the protease inhibitor antileukoprotease and the serine protease stratum corneum chymotryptic enzyme (SCCE) is coordinated in ovarian tumours" See abstract, relevant to applicant's SEQ ID NO 25	1-5, 7, 9-11, 16-20, 22, 25-27, 31-42, 62-69

C (Continuation 2)	DOCUMENTS CONSIDERED TO BE RELEVANT	
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Laval S et al (1994) Cell Growth Differ 5(11), 1173-83 "Isolation and characterization of an epithelial-specific receptor tyrosine kinase from an ovarian cancer cell line" See whole document, relevant to applicant's SEQ ID NO 27	1-5, 7, 9-11, 16-20, 22, 25-27, 31-42, 62-69
PX	WO 03 068054 A2 (THE GOVERNMENT OF THE UNITED STATES OF AMERICA as represented by THE SECRETARY, DEPARTMENT OF HEALTH SERVICES) 21 August 2003 See in particular table 1, pg 22/60 EDDR1: pg 32/60 TOP2A: 29/60 PAX8 and 33/60 SFRP4 (applicant's SEQ ID NOs 27, 29, 43 and 69)	1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 45, 47, 51-53, 62-69
X	Koshiyama M et al (2001) Anticancer Res 21, 2925-32 "Immunohistochemical expression of topoisomerase II alpha (TopII alpha) and multidrug resistance-associated protein (MRP), plus chemosensitivity testing, as chemotherapeutic indices of ovarian endometrial carcinomas" See whole document, relevant to applicant's SEQ ID NO 29	1-5, 7, 10-12, 16-20, 22, 26, 27, 31-40, 42, 43, 62-69
X	Gotlieb WH et al (2001) Gynecol Oncol 82(1), 99-104 "Topoisomerase II immunostaining as a prognostic marker for survival in ovarian cancer" See whole document, relevant to applicant's SEQ ID NO 29	1-5, 7, 10-12, 16-20, 22, 26, 27, 31-40, 42, 43, 62-69
X	Costa MJ et al (2000) Int J Gynecol Pathol 19(3), 248-57 "Topoisomerase II alpha: prognostic predictor and cell cycle marker in surface epithelial neoplasms of the ovary and peritoneum" See whole document, relevant to applicant's SEQ ID NO 29	1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 62-69
X	DGENE Abstract Accession No ABQ54317 & WO 02 00677 A1 (HUMAN GENOME SCIENCES, INC.) 3 January 2002 See abstract and claim 1, SEQ ID NO 197 (applicant's SEQ ID NO 31 reverse complement)	1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 60-69
PX	DGENE Abstract Accession No ACA03948 & US 2002/0192678 A1 (CHEN H-M) 19 December 2002 See abstract and example 13, pages 98-99 (applicant's SEQ ID NO 33)	1-5, 7, 10-12, 16-20, 22, 24-27, 31-43, 62-69

C (Continuation 3) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Medline Abstract 11925933 Sakamoto M et al (2001) Hum Cell 14(4), 305-15 "Analysis of gene expression profiles associated with cisplatin resistance in human ovarian cancer cell lines and tissues using cDNA microarray" See whole document, relevant to applicant's SEQ ID NO 35	1-5, 7, 10-12, 16-20, 22, 24-27, 31-43, 62-69
X	DGENE Abstract Accession No ABQ54876 & WO 02 00677 A1 (HUMAN GENOME SCIENCES, INC.) 3 January 2002 See abstract and claim 1, SEQ ID NO 756 (applicant's SEQ ID NO 39)	1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 60-69
X	DGENE Abstract Accession No ABL83226 & WO 01 92581 A2 (CORIXA CORPORATION) 6 December 2001 See abstract and claim 1, SEQ ID NO 6204 (applicant's SEQ ID NO 41)	1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 60-69
X	Genbank Accession No AK075046 3 September 2002 Isogai T et al *Homo sapiens* cDNA FLJ90565, clone OVARC1001336 See "features" (applicant's SEQ ID NO 50)	1-5, 7, 16-20, 22, 31-40, 62-67
X	DGENE Abstract Accession No AAH83197 & WO 01 51513 A2 (CORIXA CORPORATION) 19 July 2001 See abstract and claim 5, SEQ ID NO 821 (applicant's SEQ ID NO 52)	1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 60-69
X	DGENE Abstract Accession No ABL90699 & WO 01 90304 A2 (HUMAN GENOME SCIENCES) 29 November 2001 See abstract and claim 4, SEQ ID NO 1261 (applicant's SEQ ID NO 53)	1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 60-69
X	DGENE Abstract Accession No AAZ77553 & WO 99 53040 A2 (METAGEN GESELLSCHAFT F R GENOMFORSHUNG) 21 October 1999 See abstract, claim 3 and page 226 (applicant's SEQ ID NO 57)	1-5, 7, 10-12, 15-20, 22, 25-27, 30-43, 60-69
X	DGENE Abstract Accession No ABL67667 & WO 01 94629 A2 (AVALON PHARMACEUTICALS) 13 December 2001 See abstract and claim 1, SEQ ID NO 6004 (applicant's SEQ ID NOs 59, 60)	1-5, 7, 10-12, 15-20, 22, 25-27, 30-43, 60-69

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU03/01166

C (Continuation 4) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DGENE Abstract Accession No ABL61830 & WO 01 94629 A2 (AVALON PHARMACEUTICALS) 13 December 2001 See abstract and claim 1, SEQ ID NO 167 (applicant's SEQ ID NOs 61, 62)	1-5, 7, 10-12, 15-20, 22, 24-27, 30-43, 62-69
X	DGENE Abstract Accession No AAV64871 & WO 98 48010 A1 (GARVAN INSTITUTE OF MEDICAL RESEARCH) 29 October 1998 See Abstract and figure 3B, example and pg 22 line 34 of WO 98 48010 (applicant's SEQ ID NO 63)	1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 45, 47, 51-53, 60-69
X	DGENE Abstract Accession No ABV34360 & WO 01 60860 A2 (MILLENIUM PREDICTIVE MEDICINE, INC) 23 August 2001 See Abstract, claim 1, pg 19 and pg 7222 (applicant's SEQ ID NO 65)	1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 45, 47, 51-53, 60-69
X	DGENE Abstract Accession No ABQ54583 & WO 02 00677 A1 (HUMAN GENOME SCIENCES, INC.) 3 January 2002 See in particular abstract and claim 1, SEQ ID NO 463 (applicant's SEQ ID NO 67)	1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 45, 47, 51-53, 60-69
X	DGENE Abstract Accession No ABL62031 & WO 01 94629 A2 (AVALON PHARMACEUTICALS) 13 December 2001 See abstract and claim 1, SEQ ID NO 368 (applicant's SEQ ID NOs 73, 74)	1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 45, 47-53, 60-69
X	DGENE Abstract Accession No AAI99253 & WO 01 55313 A2 (HUMAN GENOME SCIENCES, INC) 2 August 2001 See abstract, example 2 and SEQ ID NO 1017 (applicant's SEQ ID NO 77)	1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 45, 47, 51-53, 60-69
X	DGENE Abstract Accession No ABL64081 & WO 01 94629 A2 (AVALON PHARMACEUTICALS) 13 December 2001 See abstract and claim 1, SEQ ID NO 2418 (applicant's SEQ ID NO 79)	1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 45, 47-53, 60-69

C (Continuation 5) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DGENE Abstract Accession No ABL66499 & WO 01 94629 A2 (AVALON PHARMACEUTICALS) 13 December 2001 See abstract and claim 1, SEQ ID NO 4836 (applicant's SEQ ID NO 81)	1-5, 7, 10-12, 16-20, 22, 24-27, 31-43, 45, 47, 51-53, 60-69

Box I **Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos :

   because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos : **70-73**

   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

   The claims are not limited to the technical features of the invention as disclosed in, and supported by, the specification. The claims relate to methods of assessing the promoter regions of specific genes with respect to hypermethylation and ovarian cancer. However the specification only discloses sequences derived from cDNA clones and does not disclose any promoter sequences.

3. ☐ Claims Nos :

   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II **Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

See supplementary sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:**2-5, 7, 9, 15, 19, 20, 22, 24, 30, 45 and 47-50 in full and claims 1, 10-12, 16-18, 25-27, 31-43, 51-53 and 60-69 as they relate to table 3.**

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU03/01166

Supplemental Box
(To be used when the space in any of Boxes I to VIII is not sufficient)

Continuation of Box No: II

The application claims more than one invention. Rule 13.1 of the PCT states the principle that an International Application should relate to only one invention or, if there is more than one invention, that the inclusion of those inventions in one International Application is only permitted if all inventions are so linked as to form a single general inventive concept.

Rule 13.2 of the PCT defines the method for determining whether the requirement of unity of invention is satisfied in respect of a group of inventions claimed in an International application. Unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding "special technical features." The expression "special technical features" is defined in Rule 13.2 as meaning those technical features that define a contribution which each of the inventions, considered as a whole, makes over the prior art. The determination is made on the contents of the claims as interpreted in light of the description and drawings (if any).

The claims and the description relate to methods for the diagnosis, prediction and treatment of ovarian cancer, using gene and peptide sequences whose expression is altered in ovarian cancer. In particular the claims define methods relating to the use of over 693 specific gene and/or peptide sequences.

Although all of the claims share the common feature that they all relate to methods or apparatus that involve the use of specific gene or peptide sequences whose expression is altered in ovarian cancer, this feature is known (see the documents listed below). As such this feature cannot be regarded as a special technical feature and cannot confer unity on the inventions relating to the use of specific gene or peptide sequences for the detection or treatment of ovarian cancer.

D1 US 5 912 142
D2 US 6 268 165
D3 WO 01 21653
D4 Bayani et al (2002) Cancer Research 62, 3466-76

Furthermore, there is nothing in the specification to suggest that the genes can be further divided into groups, where sequences within a group share a common special technical feature. Although the specification discloses that some of the genes can be classified into further, narrower groups, these further divisions also cannot be regarded as special technical features. These divisions correspond to groups of genes that are down-regulated or up-regulated in cancers and genes that are associated with specific types of ovarian cancers, such as epithelial or mucinous ovarian cancer. However these groups are known, as are methods of using genes specifically associated with these narrower groups for the treatment and detection of specific subsets of ovarian cancers. See in particular D4

Although there is a lack of unity the ISA has searched, as a service to the applicant, five sets of ten sequences for five search fees.

These sequences comprise SEQ ID NOS 1- 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 46, 48, 50, 52, 53, 55, 57, 59, 60- 63, 65, 67, 69, 71-75, 77, 79, 81, 83.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/AU03/01166

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	0200677	AU	29508/01	AU	30958/01	AU	36459/01
		AU	36460/01	AU	36461/01	AU	36462/01
		AU	36463/01	AU	36464/01	AU	36465/01
		AU	36466/01	AU	37943/01	AU	37944/01
		AU	37947/01	AU	37949/01	AU	37950/01
		AU	37951/01	AU	37952/01	AU	37953/01
		AU	37954/01	AU	37955/01	AU	37957/01
		AU	37958/01	AU	38585/01	AU	39726/01
		AU	39727/01	AU	39728/01	AU	41402/01
		AU	41403/01	AU	41404/01	AU	41405/01
		AU	41406/01	AU	41407/01	AU	41408/01
		AU	41409/01	AU	41410/01	AU	41411/01
		AU	41412/01	AU	41413/01	AU	41414/01
		AU	41415/01	AU	41416/01	AU	41417/01
		AU	41418/01	AU	41419/01	AU	43134/01
		AU	43135/01	AU	43136/01	AU	43137/01
		AU	45262/01	AU	45354/01	AU	47190/01
		AU	47191/01	AU	49052/01	AU	49053/01
		AU	49054/01	AU	50767/01	AU	50768/01
		AU	50769/01	AU	50770/01	AU	50771/01
		AU	50772/01	AU	52878/01	AU	52879/01
		AU	55162/01	AU	57912/01	AU	60969/01
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CA	2398275	CA	2398411	CA	2398877
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EP	1252302	EP	1252303	EP	1252312
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EP	1254157	EP	1254165	EP	1254170
EP	1254171	EP	1254172	EP	1254173
EP	1254217	EP	1254218	EP	1254219
EP	1254228	EP	1254242	EP	1254248
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EP	1259642	EP	1261380	EP	1261618
EP	1261619	EP	1261633	EP	1261634
EP	1261635	EP	1261637	EP	1261703
EP	1261742	EP	1261745	EP	1263944
EP	1265910	EP	1268527	US	2002042096
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US	2002102638	US	2002119919	US	2002120103
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		US	2003175739	US	2003190707	WO	0154472
		WO	0154473	WO	0154474	WO	0154708
		WO	0154733	WO	0155162	WO	0155163
		WO	0155164	WO	0155167	WO	0155168
		WO	0155173	WO	0155200	WO	0155201
		WO	0155202	WO	0155203	WO	0155204
		WO	0155205	WO	0155206	WO	0155207
		WO	0155208	WO	0155300	WO	0155301
		WO	0155302	WO	0155303	WO	0155304
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		WO	0155329	WO	0155343	WO	0155350
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		WO	0155368	WO	0155387	WO	0155388
		WO	0155430	WO	0155440	WO	0155441
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		WO	03025138	WO	03042661		
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